# Mandibular cortical bone evaluation on cone beam computed tomography images of patients with bisphosphonate-related osteonecrosis of the jaw

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**Objectives.** The objective of this study was to develop a technique for detecting cortical bone dimensional changes in patients with bisphosphonate-related osteonecrosis of the jaw (BRONJ).

**Study Design.** Subjects with BRONJ who had cone-beam computed tomography imaging were selected, with age- and gender-matched controls. Mandibular cortical bone measurements to detect bisphosphonate-related cortical bone changes were made inferior to mental foramen, in 3 different ways: within a fixed sized rectangle, in a rectangle varying with the cortical height, and a ratio between area and height.

**Results.** Twelve BRONJ cases and 66 controls were evaluated. The cortical bone measurements were significantly higher in cases than controls for all 3 techniques. The bone measurements were strongly associated with BRONJ case status (odds ratio 3.36-7.84). The inter-rater reliability coefficients were high for all techniques (0.71-0.90).

**Conclusions.** Mandibular cortical bone measurement is a potentially useful tool in the detection of bone dimensional changes caused by bisphosphonates. (Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:695-703)

Long-term administration of bisphosphonates (BPs) affects bone quality and metabolism following accumulation in bone.[1] Since the first cases of bisphosphonate-related osteonecrosis of the jaw (BRONJ) were published in 2003,[2] there has been a search for factors that can predict the onset of the condition. Oral and intravenous BPs reduce bone resorption, increase mineral content of bone, and alter bony architecture.[3-6] Previous studies have demonstrated these changes both radiographically and following histologic analysis.[1,3,7-10] The BP-related jaw changes may present radiological features, such as thickening of lamina dura and cortical borders, diffuse sclerosis, and narrowing of the mandibular canal[3,11]; however, oral radiographs of patients taking BPs do not consistently show radiographic changes to the jaws.[11,12] The challenge is to find imaging tools that could improve the detection of changes in the bone associated with BP use.

Various skeletal radiographic features associated with BRONJ in conventional periapical and panoramic radiographs, computed tomography, magnetic resonance imaging, and nuclear bone scanning have been described.[3,8-11] There has also been a search for BP-related quantitative methods for the evaluation of radiographic images, to avoid observer subjectivity in interpretation. Factors thought to be important include trabecular and cortical structure, and bone mineralization.[4] Consequently, measurable bone data have been reported in subjects taking BPs through many techniques, including bone density, architecture, and cortical bone thickness.[1,4,7,13] Trabecular microarchitecture of postmenopausal women has been evaluated with noninvasive techniques, such as high-resolution magnetic resonance images showing less deterioration of the bone 1 year after initiation of oral BP therapy.[4] A decrease in bone turnover and a trend for an increase in the bone wall thickness has been detected by histomorphometry in subjects taking BPs.[1] Alterations in the cortical structure of the second metacarpal have been detected in digital x-ray radiogrammetry of postmeno-

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pausal women treated with BPs.[7] Mandibular cortical width may be measured on dental panoramic radiographs, and it has been suggested as a screening tool for referring patients for bone densitometry for osteoporosis investigation.[14,15]

Inhibition of the intracortical bone remodeling in the mandible of mice taking BPs has been reported.[16] Thus, imaging evaluation of the mandibular cortical bone could be a biologically plausible way to detect BP bone alterations. Computed tomography can assess both cortical and trabecular bone characteristics. Cone-beam computed tomography (CBCT) can provide 3-dimensional information, while using lower doses and costing less than conventional CT. The CBCT images have been studied as a tool for the measurement of trabecular bone in patients with BRONJ.[13] Therefore, cortical bone measurements on CBCT of the jaws might also help to understand bone changes in patients with BRONJ.

There is no standard in quantifying dimensional changes of mandibular cortical bone. We explored several different approaches to take into consideration possible changes in length, area, and volume. These led to the 3 techniques developed in this study.

This article reports a matched case-control study in which mandibular cortical bone was measured on CBCT images of subjects with BRONJ and controls. The aim of the study was to explore the usefulness of 3 techniques for detecting mandibular cortical bone dimensional changes caused by BP.

## MATERIAL AND METHODS

All subjects with clinical features of BRONJ that had been referred to the Division of Oral Radiology, Department of Oral Medicine, of the University of Washington for CBCT imaging were selected from the archives. The goal was to have 5 gender- and age-matched controls selected for each BRONJ case, from the same archives. The use of 5 controls per case provides a substantial increase in statistical power. Images were excluded if the predetermined selected area for examination was not covered by the examination. The cases and controls were masked for the evaluation by at least 2 examiners, who were trained by one of the investigators. Each examiner independently carried out image procurement, manipulation, and subsequent measuring.

All CBCT procedures were standardized, obtained with CBCT system CB MercuRay equipment (Hitachi Medical Corporation, Tokyo, Japan), and saved into CBWorks software (version 3.0; Cybermed, Seoul, Korea). Images were realigned in a way that the inferior border, inferior to the mental foramen, was horizontal in all views (axial, sagittal, and coronal). The cortical bone was highlighted through the software tools and the mandibular cortical bone measurements were obtained using the mental foramen as an anatomical marker, on the right side. To find a method with high consistency, the measurements were obtained with 3 different techniques, and analyzed to detect differences attributable to BP-related cortical bone dimensional changes. Factors considered in this analysis were (1) the odds ratio (OR) for detecting associations between BRONJ and bone measures; (2) the reliability of the measures; and (3) biological plausibility.

### Technique 1

The mandibular cortical bone volume was calculated in a fixed-size volume of 250 $mm^3$ (10 mm $\times$ 5 mm $\times$ 5 mm) (Figure 1). Using the lined grid and the scale bar, a 10 $\times$ 5-mm rectangle was positioned on the lower border of the mandible, tangentially to the inferior border, inferior to the mental foramen, on the coronal plane. On the axial plane, a 10 $\times$ 5-mm rectangle was positioned using the mental foramen as a guide. The volume of cortical bone contained in the defined rectangle was automatically calculated in cubic millimeter ($mm^3$) by the software (Figure 2, *A*).

### Technique 2

The mandibular cortical bone measurements were obtained in a rectangle that had a fixed width, but varied in height relative to the lower mandibular cortical height. An area 15 $\times$ 5 mm was selected and positioned using the mental foramen as a guide, on the axial plane. On the coronal plane, the lower border of the rectangle was positioned tangentially to the mandibular inferior border, inferior to the mental foramen, and the upper border of the rectangle was positioned tangentially to the internal border of the cortical bone. Both the volume (located on all planes) and the area (on the coronal plane) of the cortical bone contained in the defined rectangle were automatically calculated by the software, in cubic millimeters and square millimeters, respectively. The length tool was used to calculate the height of the cortical bone in millimeters, in the same area, on the coronal plane (Figure 2, *B*).

### Technique 3

The total mandibular cortical bone area was determined on the coronal plane, in the region of the mental foramen between the roots of the teeth. The entire mandibular bony section on the coronal plane was highlighted by the software, and the area of the cortical bone was automatically calculated by the software, in square millimeters. The height of the whole mandible was calculated with the length tool, from the lower border of the mandible to the highest point of the alveolar crest bone, in millimeters. The ratio between the area and the

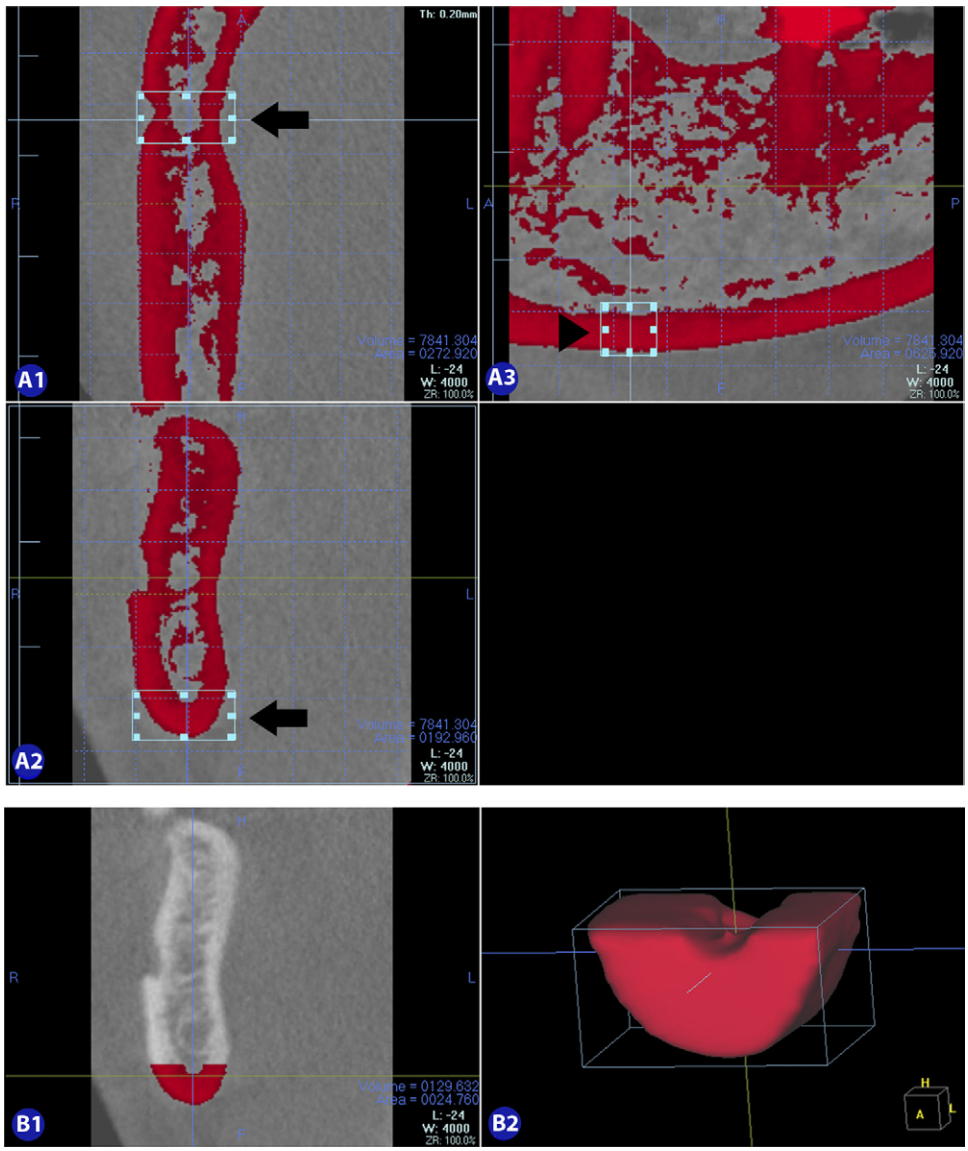


Fig. 1. Steps for acquisition of measurements for technique 1. Multiplanar reconstruction (MPR) showing the following: **A1,** axial plane—a 10 × 5-mm rectangle (*black arrow*) positioned using the mental foramen as a guide; **A2,** coronal plane—same-sized rectangle (*black arrow*) positioned with the inferior border tangential to the lower border of the cortical, inferior to the mental foramen; **A3,** sagittal plane—a 5 × 5-mm square (*arrowhead*) is automatically positioned on the lower border of the mandible. After selection of the region of interest, the volume of the cortical bone contained in the defined rectangle was calculated by the software: **B1,** coronal plane—highlighted selected region; **B2,** 3-dimensional image of the selected region.

height was used as the measurement. The software does not identify differences among different calcified structures. Thus, we eliminated from the study the images in which a root of a tooth was included, because there was not enough space between the 2 neighboring roots to avoid inclusion of parts of the root in the image (Figure 2, *C*).

Fisher and 1-way analysis of variance (ANOVA) tests were used to analyze differences between groups, for categorical and measurable variables, respectively. To establish the OR for the cortical bone measurements, the results were dichotomized in low and high cortical bone volume, area and height, respectively, using the 75th percentile in the control group as the cutoff point for each measure. The inter-rater reliability was determined by bivariate Pearson correlation. The significance level was set at .05. SPSS 10.0 software version 10 (SPSS Inc., IBM Company Headquarters, Chicago, IL) was used for storing and analyzing data. The VassarStats Web site for Statistical Computation (Richard Lowry, Poughkeepsie, NY) was used to calculate OR and its 95% confidence interval (CI).[17]

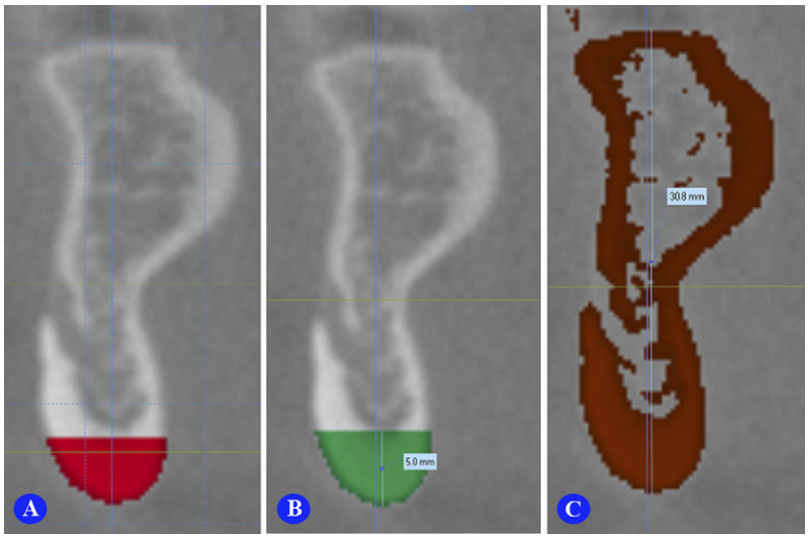


Fig. 2. Cortical bone measurements taken by 3 different techniques. **A,** Technique 1, cortical bone volume within a fixed size rectangle; **B,** technique 2, cortical bone volume, area, and height, within a rectangle that varies with the mandibular cortical height; **C,** technique 3, a ratio between the whole mandibular cortical area and the height was obtained.

The protocol was approved by the institutional review board and need for informal consent was waived. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

## RESULTS

There were 12 BRONJ cases and 66 controls preselected for the study. The demographic and radiographic characteristics of the BRONJ cases are shown in Table I. Twenty subjects were excluded because the area of the cortical bone inferior to the mental foramen was not available on the CBCT image. From the 58 subjects selected for the mandibular cortical measurements, there were 7 women and 3 men in the BRONJ group, and 34 women and 14 men in the control group. The mean ages were 63.75 (SD ±13.89) for the patients with BRONJ and 62.61 (SD ±13.54) for the controls. There was no significant difference in age ($P = .79$) or gender ($P = .61$) between the 2 groups. From the patients presenting BRONJ, 9 had the exposed bone in the mandible and 1 in the maxilla. The reasons for having the CBCT procedure in controls were implant placement (32), temporomandibular joint disorders (10), pain or numbness (2), cyst (2), tooth resorption (1), or apicoectomy (1). For technique 3, 7 more subjects were excluded because the bone space between roots was not large enough to allow measurement. Table II shows the results obtained for the cortical bone measurements and the number of studied subjects for the 3 techniques evaluated in the study.

The mean cortical bone height was significantly higher for subjects with BRONJ than for controls in all techniques (Figure 3). The cutoff points obtained for the different methods were as follows: technique 1, high cortical bone volume greater than 161.31 $mm^3$; technique 2, high cortical bone volume greater than 162.55 $mm^3$, high cortical bone area greater than 31.88 $mm^2$, high cortical bone height greater than 4.7 mm; and technique 3, high ratio cortical bone area/height greater than 6.99 mm. The odds of being a BRONJ case versus being a control were higher for an individual with higher cortical plate volume, area, thickness, and ratio of the whole mandibular cortical bone area/height.

Technique 1 showed the highest OR to detect cortical bone dimensional changes, but in many cases, the fixed vertical dimension of the rectangle did not include the total height of the cortex. In technique 2, the cortical bone height presented a good OR and a good inter-rater coefficient. Furthermore, it represented a more biologically plausible way of measuring, as it included the total height of the lower mandibular cortex.

The inter-rater reliability was tested for 31 of the subjects by 2 of the investigators (S.R.T. and E.C.A.S.), for technique 1. For technique 2, the inter-rater reliability was tested for 33 of the subjects by 3 of the investigators (S.R.T., S.P.D., and K.C.H.), and varied from 0.87 to 0.92 for the cortical bone volume; 0.66 to 0.83 for the area; and 0.87 to 0.94 for the height. The mean of the inter-rater results for technique 2 are presented in

**Table I.** Characteristics of the CBCT images of the preselected cases with BRONJ

| *Case no.* | *Gender* | *Age* | *BRONJ site* | *Bone characteristics in BRONJ site* |
|---|---|---|---|---|
| 1 | F | 63 | Right and left maxilla | Sclerotic bony pattern, with area of radiolucencies and sequestra. Borders of bilateral maxillary sinuses are also sclerotic and thick, and sinuses are filled with soft tissues. |
| 2 | F | 67 | Left mandible | Erosion and bony specula on the lingual cortical bone; widened periodontal ligament space |
| 3 | F | 68 | Right mandible | Sclerosis with osteolytic changes and a large sequestrum in the center; erosion of the lingual cortical bone |
| 4 | F | 67 | Right and left mandible | Dense bone in teeth-bearing area extending to the ramus with small osteolytic areas; nonhealed sockets on molar area; thickening of lamina dura |
| 5 | F | 43 | Left mandible | Enostosis |
| 6 | F | 49 | Left mandible | Enostosis |
| 7 | M | 59 | Left mandible | Erosion on lingual cortex |
| 8 | M | 50 | Left mandible | Extremely dense bony structure; periosteal reaction; nonhealed sockets on molar area; impacted teeth |
| 9 | F | 82 | Right mandible | Marked sclerosis; osteolysis; sequestrum |
| 10 | F | 78 | Right and left mandible | Marked sclerosis; sequestrum |
| 11 | F | 47 | Left maxilla | Massive sclerosis of alveolar process, widened periodontal ligament, and thick surrounding lamina dura |
| 12 | M | 82 | Left mandible | Widespread osteosclerotic and osteolytic changes; periosteal reaction; sequestrum |

BRONJ, bisphosphonate related osteonecrosis of the jaws; CBCT, cone-beam computed tomography; F, female; M, male.

**Table II.** Values of cortical bone measurements obtained from the 78 subjects for the 3 techniques evaluated in the study

| | *No. of cases included (excluded)* | *No. of cases initially studied by groups (excluded)* | | | | | *High/normal cortical bone* | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *BRONJ n = 12* | *Controls n = 66* | *BRONJ cases Mean ± SD* | *Controls Mean ± SD* | *P value** | *BRONJ n (%)* | *Controls n (%)* | *Odds ratio (CI) P value†* | *Inter-rater reliability‡* |
| **Technique 1** | | | | | | | | | | |
| Cortical bone volume ($mm^3$) | 58 (20) | 10 (2) | 48 (18) | 166.18 ± 34.67 | 141.65 ± 24.60 | .01 | 7/3 | 11/37 | 7.84 (1.73–35.55) .006 | 0.85 |
| **Technique 2** | | | | | | | | | | |
| Cortical bone volume ($mm^3$) | 58 (20) | 10 (2) | 48 (18) | 268.43 ± 189.54 | 135.32 ± 38.52 | <.01 | 5/5 | 11/37 | 3.36 (0.82–13.78) .09 | 0.89 |
| Cortical bone area ($mm^2$) | 58 (20) | 10 (2) | 48 (18) | 49.54 ± 31.75 | 27.69 ± 7.71 | <.01 | 5/5 | 11/37 | 3.36 (0.82–13.78) .09 | 0.71 |
| Cortical bone height (mm) | 58 (20) | 10 (2) | 48 (18) | 6.05 ± 2.18 | 4.22 ± 0.80 | <.01 | 6/4 | 11/37 | 5.04 (1.20–21.14) .02 | 0.90 |
| **Technique 3** | | | | | | | | | | |
| Ratio cortical bone area/height | 51 (27) | 9 (3) | 42 (24) | 7.47 ± 1.90 | 6.17 ± 1.23 | .01 | 5/4 | 10/32 | 4.00 (0.89–17.82) .07 | — |

BRONJ, bisphosphonates-related osteonecrosis of the jaws; CI, confidence interval.
*One-way analysis of variance.
†Fisher exact test.
‡Pearson correlation, values between 2 examiners for technique 1, and mean values between the 3 examiners for technique 2.

Table II. Inter-rater reliability was not performed for technique 3 because of the high number of subjects excluded.

To explore the association between the bone measures and the demographic factors (age and gender), we also evaluated the control group separately to check for differences in the cortical bone measurements. There was no statistically significant difference in cortical bone measurements for gender (Fisher, $P > .05$) in any of the 3 techniques. There was also no correlation of high and low cortical bone measurements with age (1-way ANOVA, $P > .05$), even when women and men were analyzed separately, in the 3 techniques.

## DISCUSSION

The present study evaluated the cortical mandibular bone in CBCT images of patients with BRONJ and controls. Three different techniques were tested initially for their reproducibility and ability to demonstrate differences in the amounts of cortical bone along the

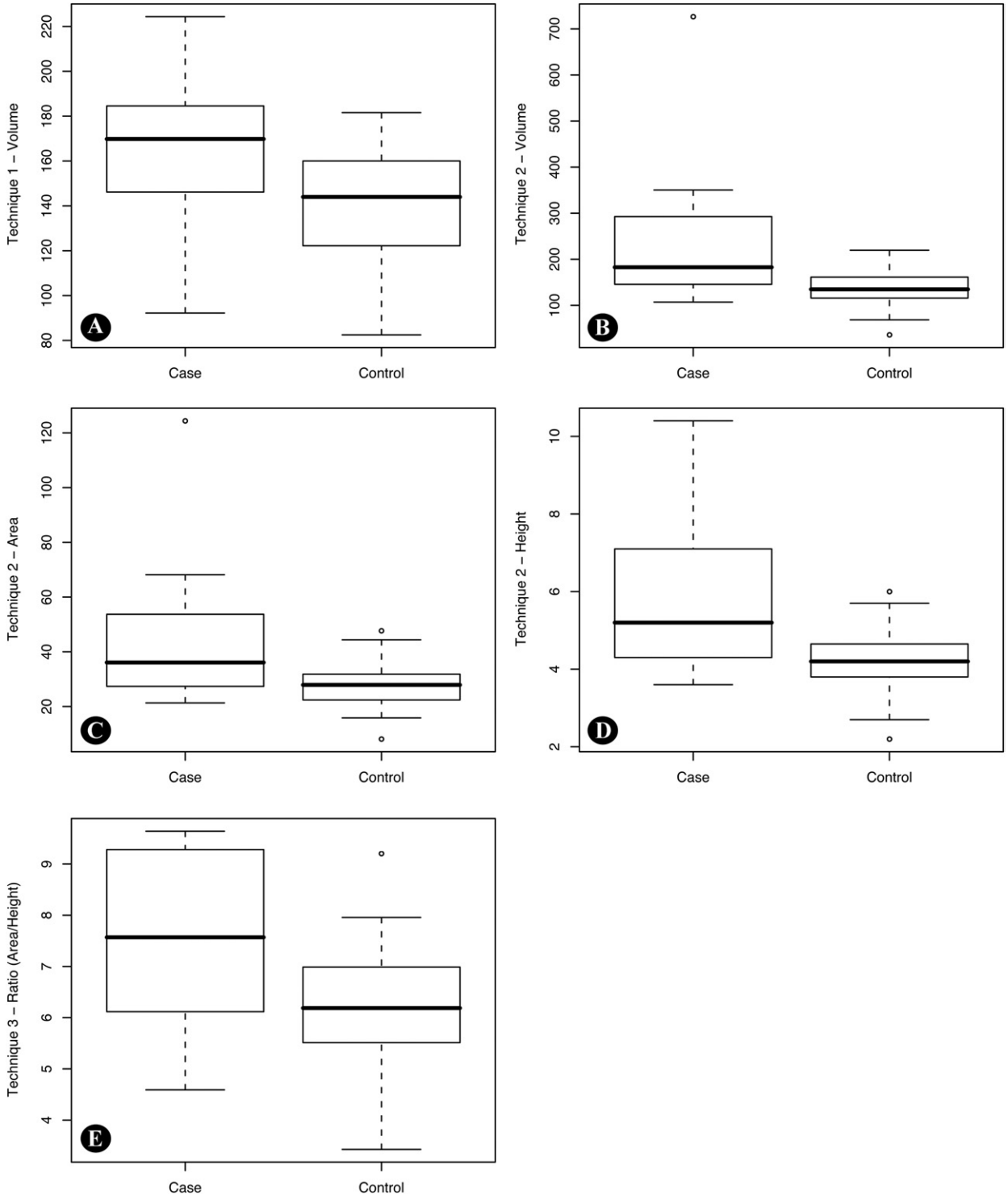


Fig. 3. Box-plot graphs of the mandibular cortical bone measurements from cases with BRONJ and controls. **A,** Cortical bone volume obtained by technique 1; **B,** cortical bone volume by technique 2; **C,** cortical bone area by technique 2; **D,** cortical bone height by technique 2; **E,** the ratio between the entire mandibular cortical area and the height obtained by technique 3. The blank circles in the graphs represent outliers, which are extreme values that deviate from the rest of the sample.

inferior borders of the mandibles. All 3 techniques were able to show BP-related mandibular cortical bone dimensional changes. The thickness of the inferior mandibular cortex in the region of the mental foramen seems to be the most promising measurement, as it showed the best reliability, high OR, and also biological plausibility, as it includes the whole mandibular cortex in the analysis. In the studied population, patients with BRONJ showed significantly higher mandibular inferior cortical bone measurements when compared with controls.

Several experimental and clinical studies have shown changes related to BP therapy in the mandibular cortex.[6,7,16,18-22] Human studies based on histomorphometry and imaging (x-ray radiogrammetry) methods have reported larger cortical thickness in patients under BP therapy.[7,19] Some case series and case reports have pointed to the cortical alterations in the images of the mandible of patients undertaking BP.[10,23,24]

The mineralized skeleton is defined externally by its periosteal surface and internally by the endosteal surface (endocortical, intracortical, and trabecular components).[25] 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.[25-27] Most of the recent studies on the pathogenesis of BRONJ point to the effect of BPs on cortical bone remodeling.[18,28] Modeling is responsible for changes in bone shape and mass during growth, whereas the main effect of remodeling is to renew existing bone.[27] In older humans, bone elongation ceases, periosteal expansion continues, and bone remodeling remains a dominant metabolic process.[29] The type of remodeling that occurs within cortical bone of humans is intracortical (osteonal).[5,20,30] Animal studies have shown that BP suppresses the endocortical and the intracortical remodeling in the mandible.[6,16,18,20,21]

It is unlikely that BP has an effect on bone modeling.[6,20] Although the periosteal bone surface can undergo remodeling, most activity on this bone surface is modeling.[6,20] In this way, BP has a positive effect on cortical bone by allowing customary periosteal growth, while reducing the rate of endocortical bone remodeling and slowing bone loss from the endocortical surface.[31] For CT-imaging, case-series studies, it was found that there is periosteal bone proliferation on the mandibles of patients with BRONJ.[10,23,24] One consideration is that the periosteal proliferation described by these authors may also be a response to other factors, such as aging or sex steroids.[32] In the CBCT images of the present study, we observed 2 cases with periosteal reaction, although it was hard to distinguish between cortical and periosteal bone on our CBCT images, especially after the mineralized structures were highlighted with the software used.

To detect dimensional changes in cortical bone, 3 techniques were investigated in this study. For the first technique, the limitation was that in many images, the endocortical border, which is one of the targets of the BP action,[33] was not included in the measurement. This technique also had the limitation of the rectangle width; so many subjects with large mandibular width had part of the cortex excluded by the "box." Even with these limitations, the odds and the reproducibility of the method were good. With technique 2, the problem of the mandible width variation was corrected, in a way that all mandibular widths would fit inside a larger rectangle, and only the height of the cortical bone varied. The measurements of volume, area, and height were obtained with good OR and reproducibility. This presented the most biologically plausible method because it included the endocortical and the periosteal borders in the analysis. Similar to the mandibular cortical thickness used to detect osteoporosis signs on panoramic radiographs,[14,15] cortical bone height on CBCT images might be a tool to detect cortical bone dimensional changes caused by BP. Technique 3 was developed so that it could possibly correct for the variations in mandibular height and width that occur in individuals. Thus, we used a ratio of the whole mandibular bone area and height. There were many images that had to be excluded from the evaluation, because there was not enough bone space between the neighboring roots to be evaluated. The software that was used does not recognize the difference between calcified structures and added the root surface area to the area of cortical bone; moreover, the calcified areas of cancellous bone were also included in the calculation by the software.

A difference in the cortical bone thickness might have been expected between individuals of different gender and age in the normal population. To verify this difference, the 48 individuals of the control group were evaluated and no difference was found in the cortical bone height for gender or for age. Because controls were age and gender matched to cases of BRONJ, the studied controls might not have represented the general population. Further studies are needed to investigate cortical bone measurements in larger healthy populations, controlling for gender and age. An additional investigation would be studying the mandibular cortex controlling for the influence of mechanical loading and the mandibular strength. The present study was not designed for that type of evaluation.

One limitation of the study was that the data on the type, dose, route, and duration of BP therapy were not available. The risk for BRONJ has been related as

dependent on time, dose, and type of BP; moreover, there was no information on the medical history of controls. As this part of the study was waived of consent, we could not collect data from the clinical files to obtain this information. For the same reason, we do not know if cortical bone differs in subjects under BP therapy who present or do not present BRONJ, and this will be the subject of our next study.

This retrospective pilot study was useful to guide the selection of the proper technique for future studies to analyze cortical bone dimensional changes related to BP. Radiologists who work with CBCT should be able to easily reproduce this methodology, as the reliability rate was high, even when performed by nonradiologist examiners. Clinicians may benefit from this measurement to detect subjects more affected by BP therapy. Future studies should focus on the prospective evaluation of subjects on different BP therapies, and the variations of cortical bone in the healthy population.

A potentially important finding of this study is that BP changes in bone structure could be detected even in areas of the mandible not compromised by the bone exposure of BRONJ. Thus, CBCT examinations of subjects taking BP might be able to show early bone alterations associated with treatment.

This result is promising, as it suggests that the dimensional changes of the cortical bone might predict BRONJ in individuals on BP therapy. To support this possibility, longitudinal studies should be performed in individuals on BP therapy. Longitudinal studies with this type of evaluation would also confirm the time-dependent effect of BP on the bone reported in preclinical studies.[6,18]

In conclusion, the evaluation of the mandibular cortical bone in the mental foramen area seems to be a useful tool in the detection of cortical bone dimensional changes caused by BPs. Technique 2 seems to be the most promising measurement for its biological plausibility, as it includes the inner and outer mandibular cortex in the analysis. This test may give an indication of possible surgical complications in patients undergoing BP therapy. Future multicenter studies are suggested, to assess larger samples and to confirm these results.

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