RESEARCH ARTICLE

Are there any differences in mandibular morphology of patients with bisphosphonate-related osteonecrosis of jaws?: a case-control study

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Objectives: The aim of this study was to compare the morphological differences in the mandible between patients with bisphosphonate-related osteonecrosis of the jaw (BRONJ) and healthy individuals and to detect the correlation between these parameters on panoramic radiography and CBCT.

Methods: The CBCT and panoramic images of patients with BRONJ ($n = 32$) and control groups ($n = 32$) were included in the study. All the comparisons were analyzed between the osteonecrosed and healthy sides of patients with BRONJ and control group. The panoramic radiographs were used to measure the values of the condyle angle, gonial angle, antegonial angle, antegonial depth, condylar height and ramal height. The mandibular cortical index (MCI) and bone quality index (BQI) were also examined on cross-sectional scans of CBCT images.

Results: There were significant differences in the MCI ($p = 0.014$) and BQI ($p = 0.021$) between the left and right side of the BRONJ group and also between the osteonecrosed side of the BRONJ and control group ($p < 0.0001$). No significant difference was found in other comparisons.

Conclusions: The outcomes of the present study indicate that bisphosphonates influenced some internal morphological changes in the mandible. These changes may be a reason of BRONJ. But, these changes are not reflective of the measured values obtained using panoramic radiographs on the external morphology of the mandible.

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Introduction

Bisphosphonates are inorganic pyrophosphates that inhibit osteoclast-mediated bone resorption and are widely used to treat metabolic and oncological diseases involving the skeleton such as metastatic bone tumours, osteoporosis, multiple myeloma and Paget's disease.¹ Bisphosphonates could have a direct anti-tumour effect, which decreases not only bone-associated events but

also advance survival.² Long-term application of bisphosphonates affects bone metabolism and quality following accumulation in the skeleton.³ One of the most severe complications of the bisphosphonate treatment is bisphosphonate-related osteonecrosis of the jaw (BRONJ). In addition, in order to reduce bone resorption, bisphosphonate raises the mineral content of the bone and alters the osseous architecture.⁴

Bisphosphonate-associated jaw alterations can show radiological findings such as diffuse sclerosis, thickening

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of the lamina dura and cortical borders and narrowing of the mandibular canal.⁵ Various skeletal radiographic features related to BRONJ in panoramic and conventional periapical radiographs, CT, nuclear bone scanning and MRI have been defined.⁴

The condyle angle (CA), gonial angle (GA), antegonial angle (AA), antegonial depth (AD), mandibular cortical index (MCI), bone quality index (BQI),⁶ ramal height (RH) and condylar height (CH)⁷ values have been used to observe different morphological conditions on two-dimensional (2D) radiography. But, for the evaluation of the MCI and BQI of patients with BRONJ, CBCT has allowed for the accurate display of the vertical and buccal–lingual dimensions as well as the important mineral density of the mandible.⁶ Some authors studied the assessment of jaw differences in BRONJ through various techniques, but none of these studies have described mandibular morphological changes in patients with BRONJ comparatively. Thus, analyzing the osseous component of the jaws on CBCT images and panoramic radiographs might also help understand bone changes that may cause BRONJ.

The purpose of this study was, therefore, to compare the typical morphological findings of BRONJ with a control group by means of measurement on combined 2D and three-dimensional (3D) techniques.

Methods and materials

In this case-control study, panoramic and CBCT images of patients with BRONJ and the external (CA, GA, AA, AD, RH and CH) and internal (MCI and BQI) morphology of the mandible were evaluated. They were compared with those of age- and gender-matched controls, who had panoramic and CBCT images performed for the treatment planning of implant-based prosthesis in the mandible.

All subjects with BRONJ were diagnosed by an oral and maxillofacial surgeon with 8 years' experience (ZBG), according to criteria of the American Association of Oral and Maxillofacial Surgeons and the American Society for Bone and Mineral Research (2007). Their panoramic radiographs (Instrumentarium OP200D digital, Tuusula, Finland; 66–85 kVp, 10–16 mA, 14.1 exposure time) and CBCT images (New Tom VG; Quantitative Radiology, Verona, Italy) had been archived in the Department of Oral and Maxillofacial Radiology, Faculty of Dentistry, Erciyes University. Flat-panel detector-based CBCT was used for imaging. The X-ray parameters (kilovoltage and milliamperage) were automatically determined from scout views by the NewTom VG. All images were obtained with the patient in the supine position. The scanning time was 18 s, collimation height was 13 cm, exposure time was 3.6 s and voxel size was 0.3 mm³. Digital imaging and communications in medicine files obtained from the CBCT scans were reconstructed using NNT viewer software (Quantitative Radiology).

Panoramic images of the mandible were used for the following measurements (Figure 1) by a digital software program (Cliniview v. 10.0.1; Instrumentarium). This computer software has a function to measure the angle and distance on the radiograph.

- (1) CA: evaluated by tracing a line tangent to the border of the ramus and another line tangent to the border of the condylar neck on each side.⁷
- (2) GA: detected by tracing a line tangent to the posterior border of the ramus and another line tangent to the lower border of the mandible on each side. The intersection of these lines formed the mandibular angle.⁷
- (3) AA: measured by tracing two lines parallel to the lower cortical border at the antegonial area and measuring the angle of their intersection at the deepest point of the antegonial notch.⁷
- (4) AD: measured as the distance along a perpendicular line from the deepest point of the antegonial notch concavity to a line parallel to the inferior cortical border of the mandible.⁷
- (5) RH, CH and RH + CH were examined on both sides; the most posterior points of the condyle and ramus of the mandible were marked as X and Y points. A line was drawn through X and Y and was called the A-line. Another line, called the B-line, was drawn from the most superior points of the condyle perpendicular to the A-line. The confluence of the A-line and B-line was called point Z. The distance between points X and Z was measured as CH. In addition to this measurement, the distance between X and Y and the distance between Z and Y were measured as RH and RH + CH, respectively. Finally, the vertical mandibular asymmetry indexes of the condyle, ramus and condyle plus ramus were calculated using the formula developed by Habets *et al.*^{8,9}

The superimposed sagittal and cross-sectional slices of the corpus of the mandible were used for the following index:

Figure 1 Panoramic radiograph with the measuring method used for the condylar angle (CA), gonial angle (GA), antegonial depth (AD), antegonial angle (AA), condylar height (CH) and ramal height (RH).

Figure 2 Appearance of the inferior mandibular cortical thickness mandibular cortical index: C1, endosteal margin of the cortex is even and sharp on both sides; C2, endosteal margin with semi-lunar defects and/or endosteal cortical residues on one or both sides; and C3, the cortical layer with heavy endosteal cortical residues and it is clearly porous.

- (6) MCI (Figure 2): mandibular cortical shapes on dental panoramic radiographs were obtained by observing the mandibles distally from the mental foramina bilaterally and by categorizing them into one of the three groups, according to the method of Klemetti *et al*,¹⁰ as follows: C1: normal cortex—the endosteal margin of the cortex was even and sharp on both sides. C2: mild to moderately eroded cortex—the endosteal margin showed semi-lunar defects (lacunar resorption) or it appeared to form endosteal cortical residues. C3: severely eroded cortex—the cortical layer formed heavy endosteal cortical residues and it was clearly porous.

The cross-sectional slices of the mental foramen area were utilized for the following index:

The superimposed cross-sectional slices of mental foramen region of the mandible were utilized the following index:

- (7) BQI: describes the bone quality based on the amount and proportion of the cortical and trabecular bone (Figure 3). The four classes are: D1, a homogeneous cortical bone; D2, a thick cortical bone with a marrow cavity; D3, a thin cortical bone with dense trabecular bone of good strength; and D4, a very thin cortical bone with low-density trabecular bone of poor strength.¹¹

The ortopantomographs and CBCT images were examined by a dentomaxillofacial radiologist independently. All the measurements were carried out by the

Figure 3 Bone quality index: D1, a homogeneous cortical bone; D2, a thick cortical bone with a marrow cavity; D3, a thin cortical bone with a dense trabecular bone of good strength; D4, a very thin cortical bone with low-density trabecular bone of poor strength.

Figure 4 Difference in the bone quality index and mandibular cortical index in both sides of the jaws in patients with bisphosphonate-related osteonecrosis of the jaw (BRONJ) and patients with BRONJ and the control group. (a) Reconstructed panoramic image of a patient with BRONJ on the left premolar region of the mandible. (a1) Class C3: cortical border on sagittal slices of right mandible; (a2) Class D3: bone quality on cross-sectional images of right mental foramen region; (a3) Class D1: bone quality on sagittal slices of left mandible; (a4) Class C1: sagittal slices of left mandible. (b) Reconstructed panoramic image of a patient in control group. (b1) Class C2: cortical border on sagittal slices of right mandible; (b2) Class D2: bone quality on cross-sectional images of right mental foramen region.

same person (GO). To study the precision of the linear measurements taken with CBCT as described above, measurements were repeated 2 weeks later, showing a high correlation. The first measurements were used for further analysis. Statistical analysis of the results was performed using SPSS for Windows SPSS® v. 16.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). An independent sample two-tailed *t*-test was used to compare the means of all the values between BRONJ and healthy sites and controls. Independent and paired samples *t*-test was carried out.

Results

There were 64 subjects enrolled in the study: 32 subjects presenting with BRONJ and 32 controls. Among the 32 patients with BRONJ (age ranged from 58–84 years), osteonecrosis were found in 14 right and 18 left sides of the mandible. However, the 14 right and 18 left sides of the 32 healthy individuals (age ranged from 60–85 years) with no systemic disorder or medication

were comprised in control group. The distribution of subjects according to age and gender included in the study are shown in Table 1. All the analyses of patients with BRONJ were performed bilaterally by separating the osteonecrosis and healthy side. The selected side of the control group was compared with the osteonecrosed site.

The values of CA, GA, AA and AD are summarized in Table 2. The mean values of CA on both sides of BRONJ are the same, but they were a bit higher in the control group. There are no significant differences in both sides of patients with BRONJ and the osteonecrosed side of patients with BRONJ compared with the control group.

The mean values of RH, CH and RH + CH measurements are demonstrated in Table 3. There are no significant differences in the osteonecrosed and healthy sides of patients with BRONJ and the control group. But, the difference of CH in both sides of patients with BRONJ is more significant, relatively.

The distribution of MCI and BQI values are summarized in Table 4. All three categories of MCI (C1, C2 and C3) were detected and category C1 was most frequently seen in BRNOJ sites. There were significant

Table 1 The distribution of patients with bisphosphonate-related osteonecrosis of the jaw (BRONJ) and control group according to age and gender

	Gender	Localization of BRONJ in the mandible			Control group		
		Right side (n = 14)	Left side (n = 18)	Total	Right side (n = 14)	Left side (n = 18)	Total
Number of patients	F	10	6	16	10	6	16
	M	4	12	16	4	12	16
Mean age of patients (years)	F	64.2	79.6	70	68.3	71.3	69.4
	M	70	71.6	71.2	70.2	69.4	69.6

F, female; M, male.

Table 2 The measurements of the condyle, gonial and antegonial angles and antegonial depth with bilateral and control group comparisons

	Condyle angle				Gonial angle				Antegonial angle				Antegonial depth			
	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD
Healthy side	159.5	174.8	168.3	3.69	135.4	159.4	146.9	7.09	146.9	178.2	163.2	7.9	0.02	0.8	0.14	0.1
<i>p</i> -value		0.9				0.2				0.8				0.2		
BRONJ side	159.7	175.8	168.3	4	131.1	148.7	148.7	8.7	150.9	177.9	163.5	7.9	0.01	2.3	0.19	0.4
<i>p</i> -value		0.1				0.9				0.6				0.5		
Control group	159.6	174.8	167	3.4	134.1	172.4	148.8	9	146.9	178.4	164.3	8.2	0.01	0.35	0.15	0.09

BRONJ, bisphosphonate-related osteonecrosis of the jaw; max, maximum; min, minimum; SD, standard deviation.

differences in the MCI between both sides of patients with BRONJ ($p = 0.014$) and between BRONJ sites and control subjects ($p < 0.0001$). The frequency of the C1 cortical border and D1 quality bone was found to be quite high in BRONJ sites. No D4 category was detected in the control group. Statistically significant differences were observed in the BQI between both sides of patients with BRONJ ($p = 0.021$) and between BRONJ sites and control subjects ($p < 0.0001$) (Figure 4).

Discussion

Bisphosphonates are appointed for a large number of conditions and diseases in which bone resorption requires to be decreased or controlled.¹² They have been proved to efficiently pressure bone resorption by inactivating osteoclasts, increase the mineral content of the bone and alter the bony architecture.¹³ The most common site for BRONJ is the alveolar bone, so that the alveolar bone appears to be the most promising site for the observation of bone alterations associated with bisphosphonates.¹⁴ Most of the recent studies on the pathogenesis of BRONJ point to the effect of bisphosphonates on histomorphologic characteristics and cortical bone remodelling of the alveolar bone in patients with BRONJ using 2D or 3D techniques.^{15–17} This is the first study on the examination of external and internal morphological changes of the mandible in patients with BRONJ by combined 2D and 3D techniques.

Radiography is usually considered as the first-line imaging modality, while CT and MRI are considered as second-line imaging modalities.¹⁴ In spite of the unreliability of the horizontal measurements, angular measurements could be composed with high credibility from the panoramic radiograph.¹⁸ Panoramic radiographs also have been proved to be appropriate for measuring the vertical symmetry of the mandible, *i.e.* RH and CH.⁸ Therefore, we measured the angles

and vertical values of the mandible on panoramic radiographs of patients with BRONJ and controls. Because of the significant differences reported in the cortical bone volume of patients with BRONJ in previous studies, the present study was predicated on the possibility of dimensional morphological differences in the mandible. The measurements of CA, GA, AA and AD were studied to evaluate the dimensional differences of dentate and edentate patients in different populations, previously.^{7,19} In these studies, significant differences were found between males and females. For this reason, the present study enrolled the same number of females and males among the patients with BRONJ and control group. But, no significant difference was found in the measurements of CA, GA, AA and AD between all groups. Other measurements for the assessment of dimensional differences in the mandible are RH and CH.^{8,9} Although these measurements are used to analyze the vertical asymmetry, in this study, the vertical values of the mandible were measured for the determination of any difference in the BRONJ sites, relatively. But, all the calculated values too showed that the differences in the RH, CH and RH + CH were not significant. These results demonstrated that changes in the balance between osteogenesis and osteolysis in BRONJ sites did not affect the external morphology of the bone.

Imaging evaluation of the mandibular bone might be a biologically reasonable way to assess bisphosphonate bone alterations. With progression of the severity of the BRONJ lesion, osteolysis of the bone also seems to be progressive, as expressed by the formation and sequestration of the new periosteal bone especially in the mandible.²⁰ Some studies in large animals and in humans have proposed that alteration is substantially higher in the jaws, especially within the intracortical²¹ component relative to other skeletal sites.¹² Clinical studies have also shown improved cortical bone thickness after bisphosphonate therapy.^{22–24} CBCT images have been studied as a tool for the measurement of the trabecular bone in patients with BRONJ.¹⁴ Therefore, the quantitative and qualitative characteristics of the mandibular bone on CBCT might also help to understand early bone alterations associated with treatment. But, in previous studies, no conclusions could be made on how radiographic features may or may not change during the development and progression of BRONJ.²⁵ In this study, the morphological differences were analyzed, which were detected in the mandibular

Table 3 The mean values of ramal and condylar measurements (in millimetres) and asymmetry indexes with bilateral and control group comparisons

Variable	Healthy side	<i>p</i> -value	BRONJ side	<i>p</i> -value	Control
RH	42.9	0.5	43.4	0.8	43.3
CH	4	0.09	3.8	0.3	4
RH + CH	47	0.1	47.3	0.9	47.2

CH, condylar height; RH, ramal height.

Table 4 The distribution of mandibular cortical index and bone quality index values with bilateral and control group comparisons

	Mandibular cortical index			Bone quality index			
	C1	C2	C3	D1	D2	D3	D4
Healthy side	13	15	4	5	7	18	2
p-value		0.014			0.021		
BRONJ side	19	11	2	22	4	5	1
p-value		<0.0001			<0.0001		
Control	8	19	5	10	11	11	0

BRONJ, bisphosphonate-related osteonecrosis of the jaw.

cortical bone border and bone density between both sides of patients with BRONJ and controls, as analyzed in CBCT. Significant differences were found not only in the MCI, but also in the BQI. A high prevalence of both C1 and D1 was observed in BRONJ sites. These results suggested that the changing of the bone mineral density in BRONJ sites may alter the patterns of cortical borders and the degree of sclerosis may be responsible for the occurrence of BRONJ. But, there is no idea about the difference between both sides of patients under bisphosphonate therapy. Further research should be performed in order to conceiving this relative tendency of one side than the other side.

References

- Orcel P, Beaudreuil J. Bisphosphonates in bone diseases other than osteoporosis. *Joint Bone Spine* 2002; **69**: 19–27. doi: [http://dx.doi.org/10.1016/S1297-319X\(01\)00336-0](http://dx.doi.org/10.1016/S1297-319X(01)00336-0)
- Brufsky AM. Bone health issues in women with early-stage breast cancer receiving aromatase inhibitors. *Curr Oncol Rep* 2008; **10**: 18–26. doi: <http://dx.doi.org/10.1007/s11912-008-0005-z>
- 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. doi: <http://dx.doi.org/10.1007/s001980050175>
- Arce K, Assael LA, Weissman JL, Markiewicz MR. Imaging findings in bisphosphonate-related osteonecrosis of jaws. *J Oral Maxillofac Surg* 2009; **67**(Suppl. 5): 75–84. doi: <http://dx.doi.org/10.1016/j.joms.2008.12.002>
- 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. doi: <http://dx.doi.org/10.1016/j.tripleo.2010.04.023>
- Tozoglu U, Cakur B. Evaluation of the morphological changes in the mandible for dentate and totally edentate elderly population using cone-beam computed tomography. *Surg Radiol Anat* 2014; **36**: 643–9. doi: <http://dx.doi.org/10.1007/s00276-013-1241-y>
- Celikoglu M, Halicioglu K, Buyuk SK, Sekerci AE, Ucar FI. Condylar and ramal vertical asymmetry in adolescent patients with cleft lip and palate evaluated with cone-beam computed tomography. *Am J Orthod Dentofacial Orthop* 2013; **144**: 691–7. doi: <http://dx.doi.org/10.1016/j.ajodo.2013.07.009>
- Habets LL, Bezuur JN, Naeiji M, Hansson TL. The ortho-pantomogram, an aid in diagnosis of temporomandibular joint problems. II. The vertical symmetry. *J Oral Rehabil* 1988; **15**: 465–71. doi: <http://dx.doi.org/10.1111/j.1365-2842.1988.tb00182.x>
- Habets LL, Bezuur JN, van Ooij CP, Hansson TL. The ortho-pantomogram, an aid in diagnosis of temporomandibular joint problems. I. The factor of vertical magnification. *J Oral Rehabil* 1987; **14**: 475–80. doi: <http://dx.doi.org/10.1111/j.1365-2842.1987.tb00742.x>
- Klemetti E, Kolmakow S, Kröger H. Pantomography in assessment of the osteoporosis risk group. *Scand J Dent Res* 1994; **102**: 68–72.
- Nackaerts O, Gijbels F, Sanna AM, Jacobs R. Is there a relation between local bone quality as assessed on panoramic radiographs and alveolar bone level? *Clin Oral Invest* 2008; **12**: 31–5. doi: <http://dx.doi.org/10.1007/s00784-007-0139-7>
- Torres SR, Chen CS, Leroux BG, Lee PP, Hollender LG, Lloid M, et al. Mandibular inferior cortical bone thickness on panoramic radiographs in patients using bisphosphonates. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015; **119**: 584–92. doi: <http://dx.doi.org/10.1016/j.oooo.2015.02.005>
- Greenspan SL, Perera S, Recker R, Wagner JM, Greeley P, Gombert BR, et al. Changes in trabecular microarchitecture in postmenopausal women on bisphosphonate therapy. *Bone* 2010; **46**: 1006–10. doi: <http://dx.doi.org/10.1016/j.bone.2009.12.025>
- Torres SR, Chen CS, 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. doi: <http://dx.doi.org/10.1259/dmfr/14636637>
- Torres SR, Chen CS, Leroux BG, Lee PP, Hollender LG, Santos EC, et al. Mandibular cortical bone evaluation on cone beam computed tomography images of patients with bisphosphonate-related osteonecrosis of the jaw. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; **113**: 695–703. doi: <http://dx.doi.org/10.1016/j.oooo.2011.11.011>
- 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. doi: <http://dx.doi.org/10.1259/dmfr.20130242>
- Koerdt S, Dax S, Grimaldi H, Ristow O, Kuebler AC, Reuther T. Histomorphologic characteristics of bisphosphonate-related osteonecrosis of the jaw. *J Oral Pathol Med* 2014; **43**: 448–53. doi: <http://dx.doi.org/10.1111/jop.12156>

This retrospective study will be useful to understand the dimensional and structural changes in the mandible for future studies to analyze bone alteration related to bisphosphonates. But, the study was limited to the cases of BRONJ that were archived at the Department of Oral and Maxillofacial Radiology at the University of Erciyes; the main limitation of this study was the fact that the bisphosphonate type, underlying disease, dose and duration of bisphosphonate therapy were not known. The risk for BRONJ has been indicated to be dependent on time, dose and type of bisphosphonates.

Conclusions

This study suggested that the osseous changes associated with BRONJ in the mandible, which includes the cortical and spongy bones, do not reflect the external morphology of the mandible on panoramic images. However, owing to the difference in the MCI and BQI, CBCT examinations of patients taking bisphosphonates before surgical procedures could be able to demonstrate the changes of the alveolar bone that may alter the treatment plan according to osseous conditions.

18. Larheim TA, Svanaes DB. Reproducibility of rotational panoramic radiography: mandibular linear dimensions and angles. *Am J Orthod Dentofacial Orthop* 1986; **90**: 45–51. doi: [http://dx.doi.org/10.1016/0889-5406\(86\)90026-0](http://dx.doi.org/10.1016/0889-5406(86)90026-0)
19. Joo JK, Lim YJ, Kwon HB, Ahn SJ. Panoramic radiographic evaluation of the mandibular morphological changes in elderly dentate and edentulous subjects. *Acta Odontol Scand* 2013; **71**: 357–62. doi: <http://dx.doi.org/10.3109/00016357.2012.690446>
20. Wilde F, Heufelder M, Lorenz K, Liese S, Liese J, Helmrich J, et al. Prevalence of cone beam computed tomography imaging findings according to the clinical stage of bisphosphonate-related osteonecrosis of the jaw. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; **114**: 804–11. doi: <http://dx.doi.org/10.1016/j.oooo.2012.08.458>
21. 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**(Suppl. 5): 61–70. doi: <http://dx.doi.org/10.1016/j.joms.2009.01.007>
22. Hyldstrup L, Jørgensen JT, Sørensen TK, Bæksgaard L. Response of cortical bone to antiresorptive treatment. *Calcif Tissue Int* 2001; **68**: 135–9. doi: <http://dx.doi.org/10.1007/s002230001204>
23. Bock O, Börst H, Beller G, Armbricht G, Degner C, Martus P, et al. Impact of oral ibandronate 150 mg once monthly on bone structure and density in post-menopausal osteoporosis or osteopenia derived from *in vivo* μ CT. *Bone* 2012; **50**: 317–24. doi: <http://dx.doi.org/10.1016/j.bone.2011.10.027>
24. 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. doi: <http://dx.doi.org/10.1007/s00198-012-1947-4>
25. Treister N, Sheehy N, Bae EH, Friedland B, Lerman M, Woo S. Dental panoramic radiographic evaluation in bisphosphonate-associated osteonecrosis of the jaws. *Oral Dis* 2009; **15**: 88–92. doi: <http://dx.doi.org/10.1111/j.1601-0825.2008.01494.x>