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RESEARCH ARTICLE

Osseous changes in patients with medication-related osteonecrosis of the jaws

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Objectives: Medication-related osteonecrosis of the jaw (MRONJ) is a severe side effect of antiresorptive agents. The aim of this study was to investigate the osseous changes in patients with MRONJ.
Methods: Cone beam CT (CBCT) images of 25 patients with MRONJ and controls were retrospectively evaluated. Buccal, lingual, apical cortical bone thicknesses; buccal, lingual, apical intracortical and cancellous bone density; diameter of mental foramen and incisive canal, and width of mental foramen were measured.
Results: Buccal and apical cortical bone thicknesses were increased; however intracortical radiodensity values decreased in the Study Group when compared with the Control Group (p = 0.007, p = 0.001). Narrowing of incisive canal was observed in patients with MRONJ (p = 0.000).
Conclusions: Clinician should have awareness about narrowing of incisive canal, apical and buccal cortical bone thickening, decreasing in cancellous bone radiodensity, and the lingual cortex destruction in patients with MRONJ.
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Introduction

Bisphosphonates (Bps) are inorganic pyrophosphates effective in inhibiting bone resorption and most widely prescribed for the treatment of patients with osteoporosis, Paget's Disease, hypercalcemia related to malignancy, multiple myeloma and symptomatic fibrous dysplasia.[1,2] Osteonecrosis of the jaw is a potentially severe side effect of antiresorptive agents including bisphosphonates with a mean incidence of 7% (0 to 27.5%) in patients treated intravenously.[3]

The American Association of Oral and Maxillofacial Surgeons (AAOMS) has updated their definition in 2014 as medication-related osteonecrosis of the jaw (MRONJ) to (1) current or previous treatment with antiresorptive or antiangiogenic agents; (2) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than 8 weeks and (3) no history of radiation therapy to the jaws or obvious metastatic disease to the jaws.[4] Accurate staging is essential to plan the correct treatment for MRONJ patients. Staging of MRONJ is currently based on the classification proposed by Ruggiero and colleagues[5] and has been adopted by AAOMS[6] (Table 1). Although clinical examination is favoured for diagnosis of MRONJ primarily, imaging is essential for determining the extent of lesion, diagnosing early stages and excluding fractures.[7] Conventional radiography and CT scans have been widely used and may show osseous changes such as periosteal reaction, sclerotic lesions, lucency and sequester formations; however, there is no golden standard.[8,9] There

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Table 1 Staging and treatment strategies of MRONJ according to AAOMS[3]

Staging of BRONJ		*Treatment modalities*
Stage 0	No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes and symptoms	Systemic management, including the use of pain medication and antibiotics
Stage 1	Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection	Antibacterial mouth rinse Clinical follow-up on a quarterly basis Patient education and review of indications for continued bisphosphonate therapy
Stage 2	Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	Symptomatic treatment with oral antibiotics Oral antibacterial mouth rinse Pain control Debridement to relieve soft tissue irritation and infection control
Stage 3	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (*i.e.* inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla) resulting in pathologic fracture, extraoral fistula, oral antral/nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor	Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement/resection for longer term palliation of infection and pain

AAOMS, American Association of Oral and Maxillofacial Surgeons; BRONJ, medication-related osteonecrosis of the jaw.

are few reports for the quantitative evaluation[10,11] of osseous changes by using cone beam CT (CBCT) and no distinct clinical-radiological systematization of MRONJ. Diagnosis of MRONJ in CBCT is usually based on classical subjective image parameters. Therefore, the aim of this study was to investigate the differences in radiological variables between the patients with MRONJ and healthy individuals in CBCT.

Material and methods

The study was approved by the Ethics Committee of Erciyes University. Sagittal, axial, and coronal CBCT scans of 25 MRONJ (*Group 1*) cases were studied. The diagnosis of MRONJ was established according to AAOMS criteria, and these cases were classified into four stages as in Table 1.[6]

The Control Group consisted of 25 patients (*Group 2*) with no history of bisphosphonate administration, and who had had CBCT scan without any radiographic alterations for other reasons (mainly for assessing bone height/width in time of pre-implant surgery). Control patients were matched by age and gender to the MRONJ patients in this study.

Measurements in CBCT

All tomography scans were obtained in supine position by using CBCT (NewTom 5G, Verona, Italy). Scanning time was 18 s, exposure time was 3.6 s, and the voxel size was 0.3 mm. Simplant Pro software (v. 13.0, Materialise HQ, Leuven, Belgium) was used to create the images and to perform the measurements, which were transformed to Digital Imaging and Communications in Medicine format. Data were reconstructed with slices at an interval of 0.25 mm.

Comparison of cortical bone thickness and bone density in mandible between patients with MRONJ and healthy individuals

Cortical bone thickness: Buccal (BW) and lingual (LW) cortical widths were measured just below the horizontal line, which was drawn under the floor of mental foramen. Apical width (AW) of cortical bone was

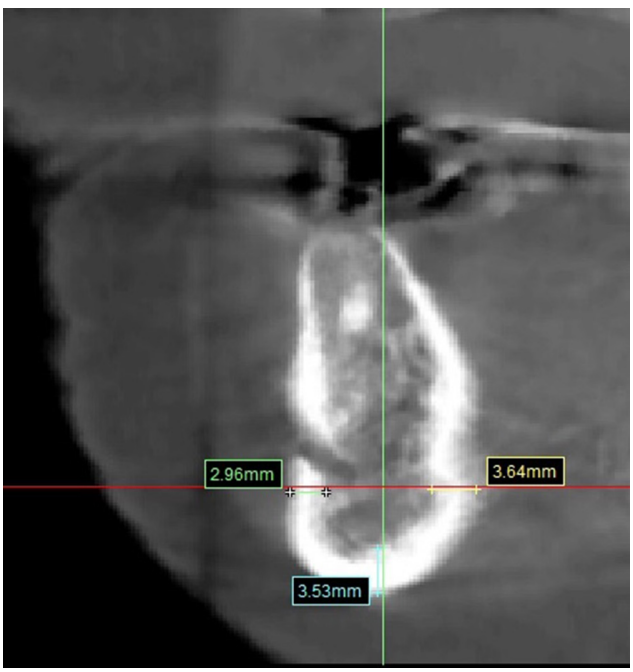

Figure 1 Coronal section of mental foramen region. Horizontal line was drawn just under the floor of the mental foramen. Buccal and lingual cortical bone thicknesses were measured below the horizontal line. Apical width of cortical bone was measured at the border of the mandible.

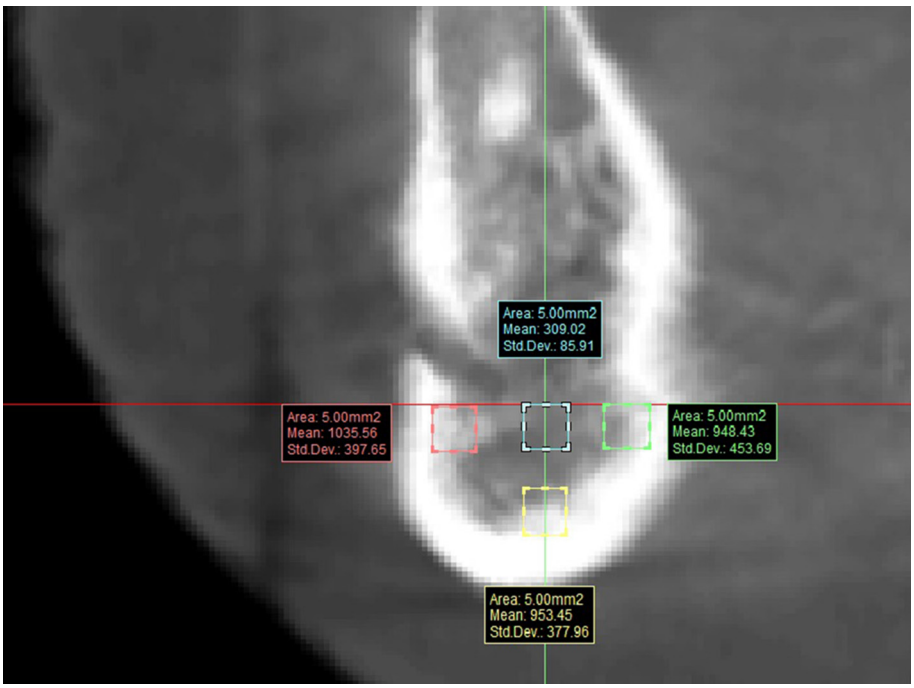

Figure 2 5 mm^2 ROI was created for the measurement of buccal (*pink*), apical (*yellow*), lingual (*green*) intracortical radiodensity values and cancellous (*blue*) radiodensity value (To view this image in colour, please refer to the online version of this paper). ROI, region of interest.

measured next to the perpendicular line at the border of the mandible (Figure 1).

Intracortical bone density value: Region of interest (ROI, 5 mm^2 square) was created for the measurement of buccal, apical and lingual intracortical bone density values (IRV). Roof of the square was located on the horizontal line and centre of the ROI was located at the intracortical region for the detection of buccal (B-IRV) and lingual intracortical radiodensity values (L-IRV). For measuring the apical IRV (A-IRV), the position of perpendicular line was at the midline of ROI (Figure 2).

Cancellous bone density values: 5 mm^2 ROI was created and roof of the square was located on the horizontal line, and midline of the ROI was positioned onto the perpendicular line for the measurement of cancellous radiodensity value (Figure 2).

Diameter and width of mental foramen

Mental foramen region was viewed from the axial and coronal sections of CBCT images of the patients. Height of the mental foramen was measured perpendicularly between the floor and roof of the foramen in coronal section (Figure 3a) and width of the foramen was measured in axial section (Figure 3b).

Diameter of incisive canal

CBCT images were viewed for the detection of the presence or absence of the mandibular incisive canal in

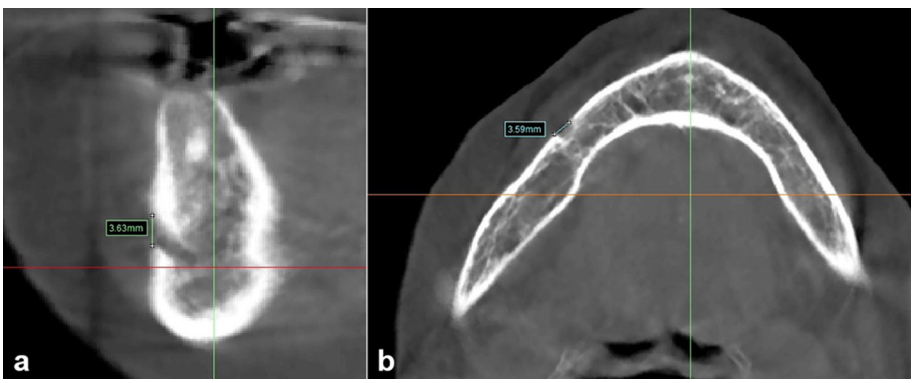

Figure 3 (a) Measurement of the height of the mental foramen between the floor and roof in coronal section; (b) measurement of the width of the foramen in axial section.

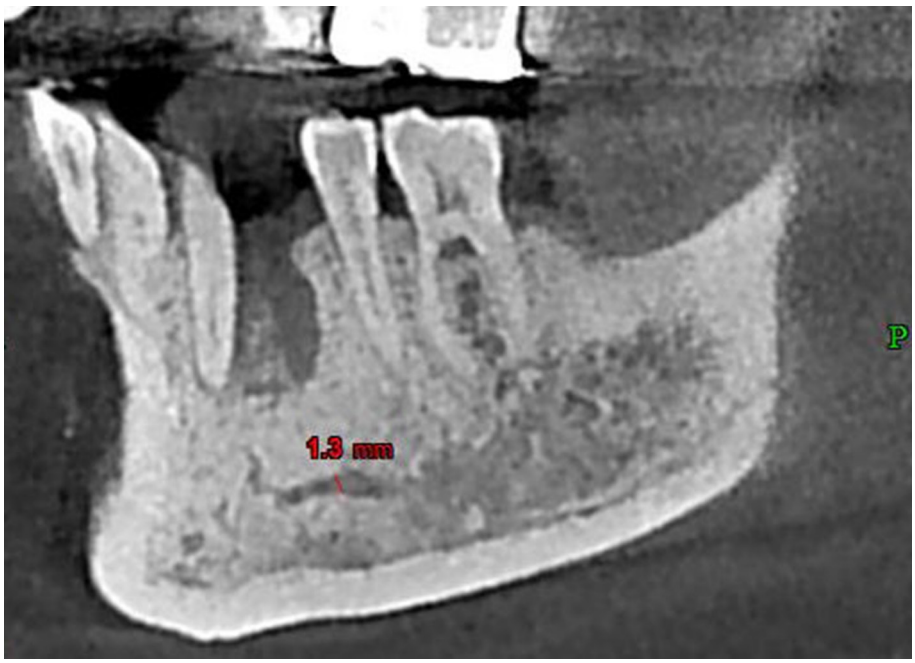

Figure 4 Incisive canal diameter was measured in sagittal section, mesial to the mental foramen.

sagittal, axial and coronal sections. After the presence of the incisive canal was confirmed, the visible length of the canal, defined as the intrabony continuation of the mandibular canal mesial to the mental foramen, was measured in the sagittal section (Figure 4) according to previous study of Şahman et al.[12]

Statistical analysis

The statistical analysis of the results was performed by using the R software, v. 3.1.1 (R Development Core Team, Vienna, Austria). Convenience of the data to the normal distribution was assessed by the Shapiro-Wilk's test, and variance homogeneity was tested by the Levene test. Two independent sample *t*-tests, and dependent two sample *t*-tests were used for the group comparisons; and one-way variance analysis was used for repeated measures. Multiple comparisons were assessed by the LSD test; and Spearman's correlation analysis was also used. A p-value < 0.05 was considered as statistically significant.

Results

The mean age of *Group 1* was 71 years (min: 46 max: 84) and 70 years (range 47–83) in *Group 2*. Out of the 25 patients studied, 14 were male and 11 were female in *Group 1*. 20 patients (80% of all patients in *Group 1*) had been used i.v. bisphosphonate and 5 patients (20%) had received oral bisphosphonate treatment. The characteristics of patients with MRONJ are listed in Table 2.

Results of comparing cortical bone thickness and bone density in mandible between patients with MRONJ and healthy individuals

25 patients in *Group 1* and 25 patients of *Group 2* were compared for measurements of cortical bone thicknesses and radiodensity at the mental foramen region (Table 3). Changes of the BW and AW, buccal and apical IRV were statistically significant ($p < 0.05$). Buccal and apical bone thicknesses were increased; however, intracortical bone density was decreased in *Group 1* when compared with the Control Group.

Results of comparing diameter and width of the mental foramen and incisive canal

Changes in diameter and width of the mental foramen were not statistically significant. The mean diameter of mental foramen was 2.69 ± 0.91 in *Group 1* and 3.05 ± 1.06 in *Group 2* ($p = 0.231$), and the mean width of mental foramen was 3.20 ± 0.76 in *Group 1* and 3.56 ± 0.78 in *Group 2* ($p = 0.128$). However, narrowing of incisive canal was observed in patients with MRONJ. Diameter of incisive foramen was 1.12 ± 0.56 mm in *Group 1* and 1.98 ± 0.64 mm in Control Group ($p = 0.000$).

Discussion

MRONJ can be developed because of the inhibitory action of the bisphosphonates (Bps) on the farnesyl synthase enzyme,[13,14] which results in loss of the ruffled border and altered cytoskeletal organization in osteoclasts. Most reported MRONJ cases use nitrogen-containing injectable Bps such as pamidronate and zoledronate.[15,16] 20 patients

Table 2 Demographic data and characteristics of patients with MRONJ

Patient	*Age*	*Sex*	*Diagnosis*	*Bisphosponate*	*Duration of treatment (months)*	*Usage*	*MRONJ localization*	*Stage*
1	64	M	Multiple myeloma	Zoledronate	4	IV	Right mandible	2
2	78	M	Lung Ca	Zoledronate	18	IV	Right mandible	2
							Left mandible	2
3	83	F	Osteoporosis	Ibandronate	48	Oral	Left mandible	2
4	78	F	Osteoporosis	Risedronate	120	Oral	Right mandible	1
5	60	M	Pancreas Ca	Zoledronate	24	IV	Left mandible	2
6	82	F	Osteoporosis	Alendronate	24	Oral	Left mandible	2
7	81	M	Prostate Ca	Zoledronate	60	IV	Right mandible	2
8	83	M	Prostate Ca	Zoledronate	48	IV	Right maxilla	2
9	77	F	Osteoporosis	Zoledronate	48	IV	Right mandible	3
							Left mandible	3
10	71	F	Breast Ca	Ibandronate	48	Oral	Right mandible	1
11	53	F	Breast Ca	Zoledronate	12	IV	Left maxilla	2
12	78	M	Prostate Ca	Zoledronate	36	IV	Left mandible	2
13	45	F	Breast Ca	Zoledronate	36	IV	Left maxilla	3
14	59	F	Breast Ca	Ibandronate	36	Oral	Left maxilla	0
15	84	M	Prostate Ca	Zoledronate	60	IV	Right maxilla	2
16	69	F	Osteoporosis	Zoledronate	1	IV	Right maxilla	0
							Left maxilla	2
17	59	F	Ovary + Endometrium Ca	Zoledronate	36	IV	Right mandible	3
18	74	M	Prostate Ca	Zoledronate	24	IV	Right mandible	2
19	70	M	Prostate Ca	Zoledronate	60	IV	Left mandible	2
							Left maxilla	0
20	58	M	Prostate Ca	Zoledronate	8	IV	Right mandible	2
21	78	M	Prostate Ca	Zoledronate	36	IV	Right mandible	3
							Left maxilla	2
22	78	M	Prostate Ca	Zoledronate	36	IV	Right mandible	2
							Right maxilla	3
23	66	F	Breast Ca	Zoledronate	48	IV	Right mandible	3
24	59	M	Prostate Ca	Zoledronate	42	IV	Left mandible	2
25	76	M	Prostate Ca	Zoledronate	48	IV	Left mandible	2

MRONJ, medication-related osteonecrosis of the jaw.

(80% of all patients in *Group 1*) had used i.v. Bp and 5 patients (20%) had used oral Bp treatment in this study; and zoledronate was the common prescribed i.v. Bp. In the case of zoledronate, the literature reports a mean of 9.3 months of administration for the promotion of MRONJ.[17] Total period of administration was in a large interval in this study, and one of the MRONJ patients (patient no: 16) had 1-month zoledronate therapy.

According to the literature, the mandible is the most affected bone in the maxillofacial region at a 2:1 proportion compared with the maxilla.[5] In this study, 68% of the MRONJ occurred in mandible.

There are few reports about the quantitative evaluation of early radiographic bone changes in MRONJ patients.[18,19] OPG, CBCT and CT may be useful to detect radiological findings in MRONJ.[11,20–23] Diagnosis of MRONJ in CBCT is usually based on classical subjective image parameters such as the detection of osteosclerosis, areas of osteolysis, cortical erosion, increased periosteal bone formation, and sequestration, potential fistula track formation and incomplete extraction socket healing.[23,24] There are several studies in the literature that have shown changes related to Bp therapy in the mandibular cortex.[25–27] Torres et al[28] reported that mandibular cortical width was higher in patients with osteonecrosis from CBCT images. They suggested that mandibular cortex width could be used to detect early changes related to treatment with Bps and to predict the risk of developing osteonecrosis of the jaws. Diniz-Freitas et al[29] found that mandibular cortical width was significantly greater in osteoporosis patients who were treated with Bps than in the Controls in CBCT. Aforementioned studies evaluated the mandibular cortex width which was called the apical cortical width (AW) in this study. AW was measured from buccal, apical and lingual for comparing the thicknesses. It was found that cortical bone became thicker in *Group 1* than healthy Controls, which is similar to the literature. BW and AW were significantly increased in *Group 1* than in the Control Group.

Table 3 Cortical bone thickness (BW, AW, LW), diameter of incisive canal and mental foramen, width of mental foramen and radiodensity values in mandible between MRONJ patients and healthy individuals

Groups	*BW (mm)*	*AW (mm)*	*LW (mm)*	*Diameter of incisive canal (mm)*	*Diameter of mental foramen (mm)*	*Width of mental foramen (mm)*	*B- IRV (HU)*	*A-IRV (HU)*	*L –IRV (HU)*	*CRV (HU)*
Group 1 (n = 25)	2,82 ± 0.77	3,62 ± 1.10	2,71 ± 0,99	1,12 ± 0.56	2,69 ± 0.91	3.20 ± 0.76	1108,50 ± 262.62	1279 1279,18 ± 357.53	1188,04 ± 251.57	666,41 ± 329.50
Group 2 (n = 25)	2,25 ± 0.50	2,62 ± 0.67	2,36 ± 0.72	1,98 ± 0.64	3,05 ± 1.06	3.56 ± 0.78	1283,11 ± 224.94	1482,92 ± 222.33	1185,97 ± 242.96	714,27 ± 254.86
P value	0.007[a]	0.001[a]	0.185	0.000[a]	0.231	0.128	0.019[a]	0.023[a]	0.977	0.582

AW, apical width; BWbuccal width; CRV, cancellous radiodensity value; HU, Hounsfield unit; LW, linguaalwidth; MRONJ, medication-related osteonecrosis of the jaw.
[a]Data were expressed as mean ± standard deviation.

The bone turnover is more rapid in cancellous bone than in cortical bone.[30] Hamada et al[10] reported the cancellous bone CT radiodensity value was a good indicator for the sensitive detection of changes in bone, and for the early detection of MRONJ.

Cankaya et al[1] suggested using Hounsfield unit (HU) to be efficient in the diagnosis of MRONJ in CBCT, corroborating the current notion of bone density changes in the evolution of MRONJ.

The mineralized skeleton had an endosteal surface and included endocortical, intracortical and trabecular components at this internal part.[23] Most of the recent studies on the pathogenesis of MRONJ point to the effect of Bps on cortical bone remodeling.[31] Bps suppresses the endocortical and the intracortical remodelling in the mandible,[25,27] and the type of remodelling that occurs within cortical bone of humans is intracortical (osteonal).[28] In this study, the intracortical bone density value was measured, and according to the results; apical IRV and buccal IRV were statistically significant and decreased in *Group 1* when compared with the Control Group.

The mandibular canal may present narrowing in patients who receive Bp treatment.[24] Hutchinson et al[4] reported diffuse sclerosis and prominent inferior alveolar nerve with narrowing of canal margins.[19] On the other hand, Krishnan et al[7] found the inferior alveolar nerve thickening in MRI, and they showed the loss of the normal T1 hyperintensity of fatty marrow in the both mandible and maxilla in MRI. According to the results of this study, changes in diameter and width of the mental foramen were not statistically significant between Healthy Controls and MRONJ patients. However, narrowing of incisive canal was observed in patients with MRONJ.

Standard diagnosis based on clinical and radiological criteria is still lacking, and there is no clinical-radiological guideline with quantitative values (such as cut-off values) according to the stages in MRONJ for the clinicians. However, early detection may lead to efficient therapy, and may increase the life-comfort of patients. Therefore, to support this possibility, longitudinal studies should be performed in individuals with MRONJ.

In conclusion, CBCT seems to be a useful tool in the detection of cortical bone dimensional changes caused by Bps. Apical and buccal cortical bone thickening, decreasing in cancellous bone density in the same areas and narrowing of incisive canal in mandible have the potential to be a simple and quantitative method to detect the early stages of MRONJ. Future multicentre studies are suggested to assess larger samples and to confirm these results.

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References

1. Cankaya AB, Erdem MA, Isler SC, Demircan S, Soluk M, Kasapoglu C, et al. Use of cone-beam computerized tomography for evaluation of bisphosphonate-associated osteonecrosis of the jaws in an experimental rat model. *Int J Med Sci* 2011; **8**: 667–72. doi: https://doi.org/10.7150/ijms.8.667
2. Fehm T, Beck V, Banys M, Lipp HP, Hairass M, Reinert S, et al. Bisphosphonate-induced osteonecrosis of the jaw (ONJ): Incidence and risk factors in patients with breast cancer and gynecological malignancies. *Gynecol Oncol* 2009; **112**: 605–9. doi: https://doi.org/10.1016/j.ygyno.2008.11.029
3. Miksad RA, Lai KC, Dodson TB, Woo SB, Treister NS, Akinyemi O, et al. Quality of life implications of bisphosphonate-associated osteonecrosis of the jaw. *Oncologist* 2011; **16**: 121–32. doi: https://doi.org/10.1634/theoncologist.2010-0183
4. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al.American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. *J Oral Maxillofac Surg* 2014; **72**: 1938–56. doi: https://doi.org/10.1016/j.joms.2014.04.031
5. Ruggiero SL, Fantasia J, Carlson E. Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **102**: 433–41. doi: https://doi.org/10.1016/j.tripleo.2006.06.004
6. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B, et al. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws—2009 update. *J Oral Maxillofac Surg* 2009; **67**(5 Suppl): 2–12. doi: https://doi.org/10.1016/j.joms.2009.01.009
7. Krishnan A, Arslanoglu A, Yildirm N, Silbergleit R, Aygun N. Imaging findings of bisphosphonate-related osteonecrosis of the jaw with emphasis on early magnetic resonance imaging findings. *J Comput Assist Tomogr* 2009; **33**: 298–304. doi: https://doi.org/10.1097/RCT.0b013e31817e4986
8. Dore F, Filippi L, Biasotto M, Chiandussi S, Cavalli F, Di Lenarda R. Bone scintigraphy and SPECT/CT of bisphosphonate-induced osteonecrosis of the jaw. *J Nucl Med* 2009; **50**: 30–5. doi: https://doi.org/10.2967/jnumed.107.048785
9. Guggenberger R, Fischer DR, Metzler P, Andreisek G, Nanz D, Jacobsen C, et al. Bisphosphonate-induced osteonecrosis of the jaw: comparison of disease extent on contrast-enhanced MR imaging, [18F] fluoride PET/CT, and conebeam CT imaging. *AJNR Am J Neuroradiol* 2013; **34**: 1242–7. doi: https://doi.org/10.3174/ajnr.A3355
10. Hamada H, Matsuo A, Koizumi T, Satomi T, Chikazu D. A simple evaluation method for early detection of bisphosphonate-related osteonecrosis of the mandible using computed tomography. *J Craniomaxillofac Surg* 2014; **42**: 924–9. doi: https://doi.org/10.1016/j.jcms.2014.01.012
11. 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. doi: https://doi.org/10.5037/jomr.2010.1203
12. Sahman H, Sekerci AE, Sisman Y, Payveren M. Assessment of the visibility and characteristics of the mandibular incisive canal: cone beam computed tomography versus panoramic radiography. *Int J Oral Maxillofac Implants* 2014; **29**: 71–8. doi: https://doi.org/10.11607/jomi.3304
13. Rogers MJ, Frith JC, Luckman SP, Coxon FP, Benford HL, Mönkkönen J, et al. Molecular mechanisms of action of bisphosphonates. *Bone* 1999; **24**(5 Suppl): 73S–79S. doi: https://doi.org/10.1016/S8756-3282(99)00070-8
14. Assael LA. Bisphosphonates and oral health: primer and an update for the practicing surgeon. *Oral Maxillofac Surg Clin North Am* 2011; **23**: 443–53. doi: https://doi.org/10.1016/j.coms.2011.04.002
15. Marx RE, Pamidronate MRE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003; **61**: 1115–7. doi: https://doi.org/10.1016/S0278-2391(03)00720-1
16. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 2004; **62**: 527–34. doi: https://doi.org/10.1016/j.joms.2004.02.004
17. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. *J Oral Maxillofac Surg* 2005; **63**: 1567–75. doi: https://doi.org/10.1016/j.joms.2005.07.010
18. Hutchinson M, O'Ryan F, Chavez V, Lathon PV, Sanchez G, Hatcher DC, et al. Radiographic findings in bisphosphonate-treated patients with stage 0 disease in the absence of bone exposure. *J Oral Maxillofac Surg* 2010; **68**: 2232–40. doi: https://doi.org/10.1016/j.joms.2010.05.003
19. Takaishi Y, Ikeo T, Nakajima M, Miki T, Fujita T. A pilot case-control study on the alveolar bone density measurement in risk assessment for bisphosphonate-related osteonecrosis of the jaw. *Osteoporos Int* 2010; **21**: 815–25. doi: https://doi.org/10.1007/s00198-009-1021-z
20. Arce K, Assael LA, Weissman JL, Markiewicz MR. Imaging findings in bisphosphonate-related osteonecrosis of jaws. *J Oral Maxillofac Surg* 2009; **67**(5 Suppl): 75–84. doi: https://doi.org/10.1016/j.joms.2008.12.002
21. Treister NS, Friedland B, Woo SB. Use of cone-beam computerized tomography for evaluation of bisphosphonate-associated osteonecrosis of the jaws. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; **109**: 753–64. doi: https://doi.org/10.1016/j.tripleo.2009.12.005
22. 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: https://doi.org/10.1016/j.oooo.2012.08.458
23. Bedogni A, Blandamura S, Lokmic Z, Palumbo C, Ragazzo M, Ferrari F, et al. Bisphosphonate-associated jawbone osteonecrosis: a correlation between imaging techniques and histopathology. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008; **105**: 358–64. doi: https://doi.org/10.1016/j.tripleo.2007.08.040
24. 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. doi: https://doi.org/10.3174/ajnr.A0518
25. 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. doi: https://doi.org/10.1016/j.bone.2010.10.159
26. Hyldstrup L, Jørgensen JT, Sørensen TK, Baeksgaard L. Response of cortical bone to antiresorptive treatment. *Calcif Tissue Int* 2001; **68**: 135–9. doi: https://doi.org/10.1007/s002230001204
27. Recker RR, Delmas PD, Halse J, Reid IR, Boonen S, García-Hernandez PA, et al. Effects of intravenous zoledronic acid once yearly on bone remodeling and bone structure. *J Bone Miner Res* 2008; **23**: 6–16. doi: https://doi.org/10.1359/jbmr.070906
28. 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: https://doi.org/10.1259/dmfr/14636637
29. Diniz-Freitas M, Fernández-Montenegro P, Fernández-Feijoo J, Limeres-Posse J, González-Mosquera A, Vázquez-García E, et al. Mandibular cortical indices on cone-beam computed tomography images in osteoporotic women on treatment with oral bisphosphonates. *Gerodontology* 2016; **33**: 155–60. doi: https://doi.org/10.1111/ger.12121
30. Matsuo A, Chiba H, Takahashi H, Toyoda J, Hasegawa O, Hojo S. Bone quality of mandibles reconstructed with particulate cellular

bone and marrow, and platelet-rich plasma. *J Craniomaxillofac Surg* 2011; **39**: 628–32. doi: https://doi.org/10.1016/j.jcms.2011.01.003

31. 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: https://doi.org/10.1016/j.oooo.2011.11.011