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Comparison of findings of radiographic and fractal dimension analyses on panoramic radiographs of patients with early-stage and advanced-stage medication-related osteonecrosis of the jaw

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Objectives. The aim of this study was to compare the panoramic radiographs of patients with early-stage and advanced-stage medication-related osteonecrosis of the jaw (MRONJ) for differences in radiographic findings and fractal dimension (FD).

Study Design. Data were collected from the medical records of 66 patients confirmed as having MRONJ. Panoramic radiographs of 66 patients (group I; without bone exposure; and group II; with bone exposure) were evaluated for the following signs; osteolysis, cortical erosion, focal and diffuse sclerosis, sequestrum, lamina dura thickening, enhancement of the inferior alveolar canal (IAC), persistent alveolar socket, pathologic fractures, and enhancement of the external oblique ridge. FD values were also compared between groups.

Results. The signs of focal and diffuse sclerosis, sequestrum, and enhancement of the IAC were observed significantly more often in group II than group I ($P < .05$). The mean FD values were 1.42 ± 0.11 in group I and 1.44 ± 0.18 in group II and were significantly different only in 1 region but not significantly different overall.

Conclusions. Radiographic alterations of bone structures appeared more frequently in patients with advanced stages of MRONJ. No significant difference was detected in the FD values among the tested regions except the cancellous bone above the mandibular canal on the distal side of the mental foramen. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:78−86)

Bisphosphonates (BPs) are the most commonly used antiresorptive drugs administered to prevent skeletal complications associated with many diseases.[1,2] The term *bisphosphonate-related osteonecrosis of the jaw (BRONJ)* was first coined by Marx in 2003.[3] In the statements of opinion published in 2007 and 2009, the American Association of Oral and Maxillofacial Surgeons (AAOMS) defined BRONJ as "a clinical case characterized with current or previous treatment with a bisphosphonate, exposed bone in the maxillofacial region that has persisted for more than 8 weeks, and no history of radiation therapy to the jaws."[4,5] In the following years, this condition was also reported to be caused by antiresorptive drugs (e.g., denosumab) and antiangiogenic drugs (e.g., bevacizumab and sunitinib), thus prompting the AAOMS to change the name to the broader "medication-related osteonecrosis of the jaw" (MRONJ) in 2014.[1]

Prevention and early diagnosis of MRONJ have been the target of investigations of these lesions. The possibility of disease occurrence without bone exposure, in turn, has been widely discussed in the literature and should be considered during patient evaluation. Several studies have investigated the diagnostic strategies for predicting the onset of MRONJ, such as analysis of serum C-terminal telopeptide and other bone turnover markers, periapical radiographs standardized by an aluminum step wedge, and measurement of thickness of the mandibular inferior cortical bone.[6-8]

Another approach can be detection of specific radiographic signs on dental panoramic radiographs.[9,10] The assumption that there are such signs to be found is based on the mode of action of antiresorptive drugs, which lead to gain of bone mass. BPs and other antiresorptive drugs increase apoptosis by inhibiting osteoclast differentiation and function, and these events cause reduced bone resorption and remodelling.[11] Although osteoclast differentiation and function play a crucial part in the remodeling of all bones in the skeletal system, osteonecrosis is most commonly observed in the maxillae and the mandible because of high bone metabolism.[12] The effect of these drugs on bone turnover, particularly in the jaws, requires the evaluation of specific radiologic signs, such as osteolysis,

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Statement of Clinical Relevance

This study demonstrated that there was no significant difference between groups in terms of mean fractal dimension values. Focal and diffuse sclerosis, sequestrum, and enhancement of the inferior alveolar nerve canal were significantly more prevalent in patients with advanced-stage medication-related osteonecrosis of the jaw.

osteosclerosis, dense woven bone, a thickened lamina dura, subperiosteal bone deposition, and failure of postoperative remodeling.[13] The correct and early diagnosis of patients with MRONJ and the identification of parameters associated with the development of bone exposure are of importance in management. Determining early radiographic changes in patients using bisphosphonates or other antiresorptive drugs can help dentists and clinicians plan appropriate treatment and prevent osteonecrosis in patients with MRONJ.

Current digital technology and image analysis methods allow for the measurement of changes in the alveolar bone.[14] The use of fractal dimension (FD) analysis to describe the structure of trabecular bone has been suggested. In this method, complex shapes and structural formations, are analyzed and the value obtained from the analysis is the FD.[14] The FD is commonly used in images to evaluate and quantify cancellous bone structure for detecting bone changes, healing of periapical lesions, and systemic conditions, such as osteoporosis, diabetes mellitus, and sickle cell anemia.[15-17]

Few studies have used FD analysis to examine the changes in the bone structure of patients with MRONJ to determine if there is a correlation between disease and radiographic findings.[18,19] FD analysis is typically used with a focus on bone structure changes in healthy patients and those using BPs. To our knowledge, this is the first study investigating radiographic changes in the early stage of MRONJ by using FD dimension analysis of panoramic radiographs.

The goal of this retrospective study was to compare the panoramic radiographs of patients with early-stage (stage 0) and advanced-stage (stages 1, 2, and 3) MRONJ for differences in radiographic findings and FD. The null hypothesis stated that there were no differences in the frequency of radiographic changes or in the FD between the 2 groups of patients.

MATERIALS AND METHODS

This retrospective study covered a 5-year period (January 2013−January 2018) and considered the data, records, and panoramic radiographs of 66 patients from our faculty's databases. The inclusion criterion was having MRONJ resulting from iatrogenic causes. This study was approved by the ethical committee of our university. Diagnosis and staging were done according to the latest updated criteria released by the AAOMS in 2014.[1] In stage 0, patients had no clinical evidence of necrotic bone, but exhibited nonspecific clinical findings, radiographic changes, and symptoms. In patients in stages 1, 2, and 3, necrotic bone exposure was detected and considered an *essential* condition for the diagnosis of MRONJ.[1] Patients with a history of head and neck radiotherapy or necrotic bone areas of less than 8 weeks' duration were excluded. Data pertaining to age, gender, systemic disease, drug type, drug administration, duration of drug therapy, stage of MRONJ, location of MRONJ, local etiologic factors for necrosis, and radiologic findings were collected from patients' medical records. Clinical examination was performed by an oral and maxillofacial surgeon (O.Ş.) with experience in MRONJ cases. The patients were classified into 2 groups, according to the criteria reported by the AAOMS. Group I comprised patients without bone exposure (early stage; stage 0: 28 patients). Group II comprised patients with bone exposure (advanced stage: stage 1: 18 patients; stage 2: 16 patients; and stage 3: 4 patients, for a total of 38 patients). Of the 66 patients, 20 were men and 46 were women (Table I). Evaluation of panoramic radiographs for radiographic findings indicative of MRONJ and calculation of the FD were performed.

Radiographic findings

The panoramic images were evaluated by 2 experts with 10 years (K-Ö.D.) and 18 years (E-Ş.K-Ç.) experience in oral and maxillofacial radiology. The radiologists were aware of the antiresorptive treatment received but were blinded to the clinical situation, symptoms, and presence of bone exposure. The experts performed the radiologic evaluation by using the methodology developed by Rocha et al.[20] by dividing the jaws into segments (1, 2, 3: maxilla; 4, 5, 6: mandible) (Figure 1). The segments represented the right posterior maxilla, anterior maxilla, left posterior maxilla, right posterior mandible, anterior mandible, and left posterior mandible in numerical order. Radiographic findings were evaluated for the following: osteolysis, cortical erosion, focal and diffuse sclerosis, sequestrum, lamina dura thickening, enhancement of the inferior alveolar canal, persistent alveolar socket, pathologic fractures, and enhancement of the external oblique ridge (Figures 2, 3, and 4) The signs were marked as being present or absent in each segment. The number of segments where each variable occurred in each patient was recorded. When consensus on the radiographic assessment was not reached, the opinion of 1 author (E-Ş. K-Ç.) was used.

FD analysis

FD analysis of the digital images was conducted with Image J software version 1.3 v (National Institutes of Health, Bethesda, MD). All measurements were performed by a dentomaxillofacial radiologist (E-Ş. K-Ç.) with experience in FD analysis. Regions of interest (ROIs) were selected manually in sites where standardization would be possible by referring to an anatomic landmark for further studies. For analysis, 4

Table I. Characteristics of patients with medication-related osteonecrosis of the jaw (MRONJ)

	Group I (without bone exposure) (28 cases)	*Group II (with bone exposure) (38 cases)*	
Age (Mean age ± standard deviation)	62.72 ± 10.82; 66.21 ± 10.59	t = −0.272; P > .05	
Gender			
Males	8 (28.5%)	12 (31.5%)	P > .05
Females	20 (71.5%)	26 (68.5%)	(Fisher's exact test)
Systemic Disease			
Lung cancer	3 cases (10.7%)	4 cases (10.5%)	χ2 = 2.87; P > .05
Renal cancer	1 case (3.5%)	3 cases (7.8%)	
Breast cancer	4 cases (14.2%)	11 cases (35.5%)	
Multiple myeloma	3 cases (10.7%)	3 cases (7.8%)	
Nasopharynx cancer	1 case (3.5%)	3 cases (7.8%)	
Osteoporosis	13 cases (46.8%)	6 cases (15.7%)	
Ovarian cancer	1 cases (3.5%)	2 cases (5.2%)	
Prostate cancer	2 cases (7.1%)	6 cases (15.7%)	
Drug Type	Ibandronate: 8 cases (28.5%) Alendronate: 17 cases (60.7%) Residronate: 3 cases (10.8%)	ibandronate: 6 cases (15.7%) alendronate: 9 cases (23.6%) zoledronic acid: 15 cases (39.4%) Denosumab: 8 cases (21.3%)	χ2 = 37.70; P < .01
Route of Drug Administration			
Intravenous	4 cases (14.2%)	24 cases (63.2%)	χ2 = 15.76; P < .01
Oral	24 cases(85.8%)	14 cases (36.8%)	
Duration of Drug Therapy	21 months (1−4 years)	48 months (2−11 years)	χ2 = 9.68; P > .05
Stages of MRONJ	Stage 0: 28 cases (100%)	Stage 1: 18 cases (47.3%) Stage 2: 16 cases (42.1%) Stage 3: 4 cases (10.6%)	
Location of MRONJ			
Mandible	20 cases (71.5%)	25 cases (65.8%)	χ2 = 3.79; P > .05
Upper jaw	7 cases (25%)	12 cases (31.5.%)	
Both upper jaw and mandible	1 cases (3.5%)	1 cases (2.7%)	
Local Etiologic Factors for Necrosis			
Dental extractions	21 cases (75%)	27 cases (71.1%)	χ2 = 1.64; P > .05
Prosthesis	2 cases (7.1%)	6 cases (15.7%)	
Spontaneous	4 cases (14,3%)	4 cases (10.5%)	
Implant treatment	1 case (3.6%)	1 case (2.7%)	

different ROIs were created at the maximum possible size (72 × 72 mm^2) in the cancellous bone on each image in 4 regions: region 1: anterior to the mandibular foramen; region 2: above the supracortical area in the angle of the mandible; region 3: anterior to the mental foramen; and region 4: superior to the mandibular canal on the distal side of the mental foramen. FD was calculated separately on each side of the mandible, and the mean values were calculated. Periapical and periodontal sites were not used to avoid false interpretation caused by inflammatory alterations. FD analysis was performed on these ROIs with the box-counting method proposed by White and Rudolph.[21] The steps of the FD analysis process performed by this method were as follows (Figure 5):

- The panoramic radiographs were converted into tagged image file formats because of their high resolution. Each ROI was selected with the size of 72 × 72 pixels (see Figure 5A).

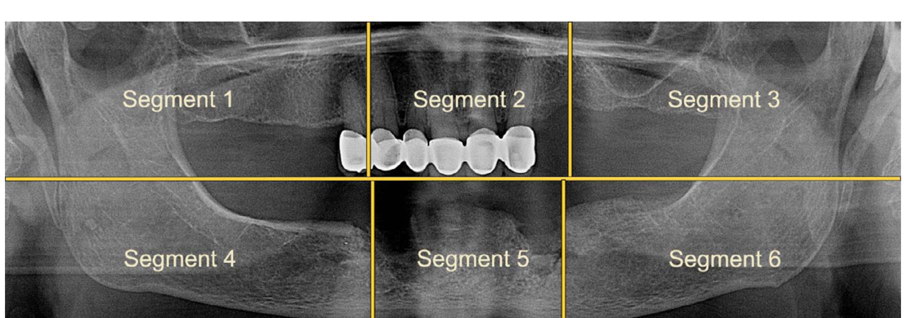

Fig. 1. Depiction of radiographic segments used for radiographic analyses.

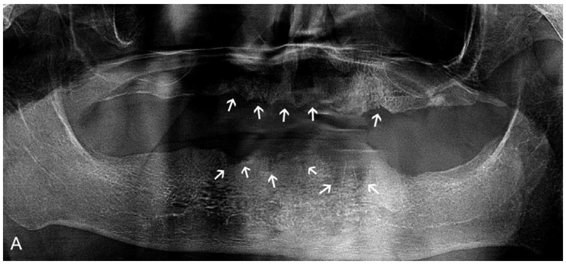

Fig. 2. Osteolytic processes at the maxilla and the mandible.

- A copy of the ROI created on the original radiograph was obtained (see Figure 5B).
- This obtained image was blurred by using a Gaussian filter. With this process, all the medium- and small-scale details were removed, leaving only large-dimensional differences on the image (see Figure 5C).
- Figure 5C was subtracted from the original image (see Figure 5B) and is shown as Figure 5D. A total of 128 was added at each pixel position. To reflect individual differences, such as trabecular and marrow spaces, an image with a minimum intensity value of 128 was created (see Figure 5E).
- The image was then rendered (segmented) to a binary (black-and-white) image by using 128 brightness threshold values. The black areas on the binary image were the radiographically representative of the trabecular bone (see Figure 5F).
- To remove noise on the image, "erode" and "dilate" operations were performed, respectively (see Figures 5G and 5H).
- As a final step in image processing, a "skeletonize" operation was performed by using "erode" processing (see Figure 5I) until 1 pixel line was left around the black areas on the image.

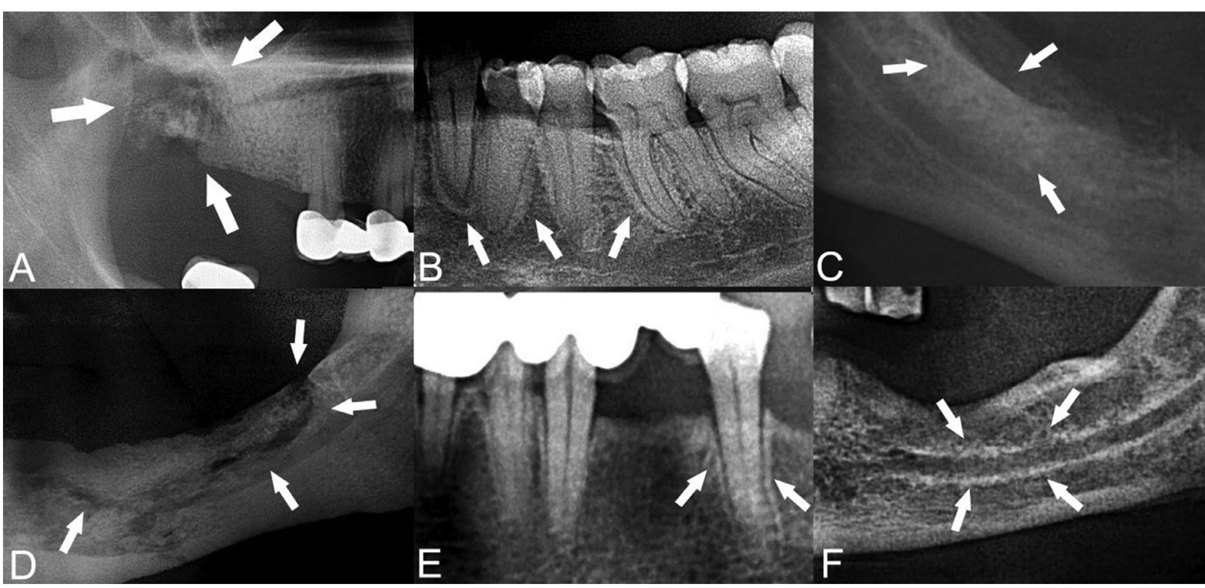

Fig. 3. **(A)** Cortical erosion. **(B)** Focal sclerosis. **(C)** Diffuse sclerosis. **(D)** Sequestrum. **(E)** Thickening of the lamina dura. **(F)** Enhancement of the inferior alveolar canal.

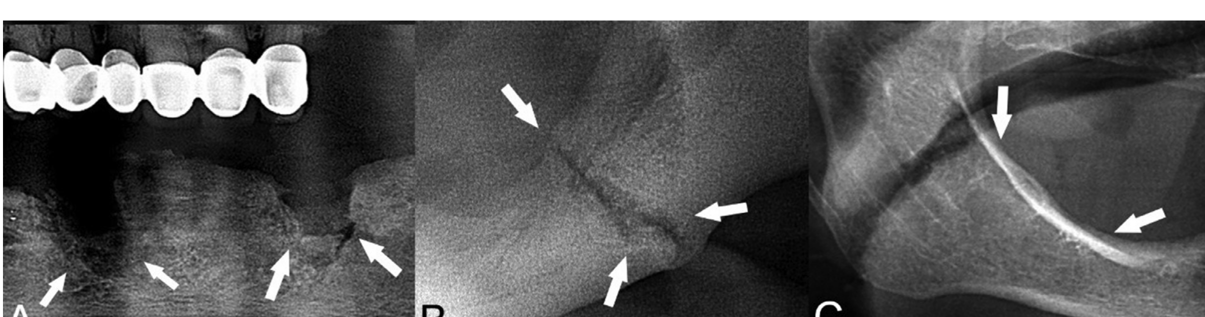

Fig. 4. **(A)** Persistent alveolar sockets. **(B)** Pathologic fracture. **(C)** Enhancement of the external oblique ridge.

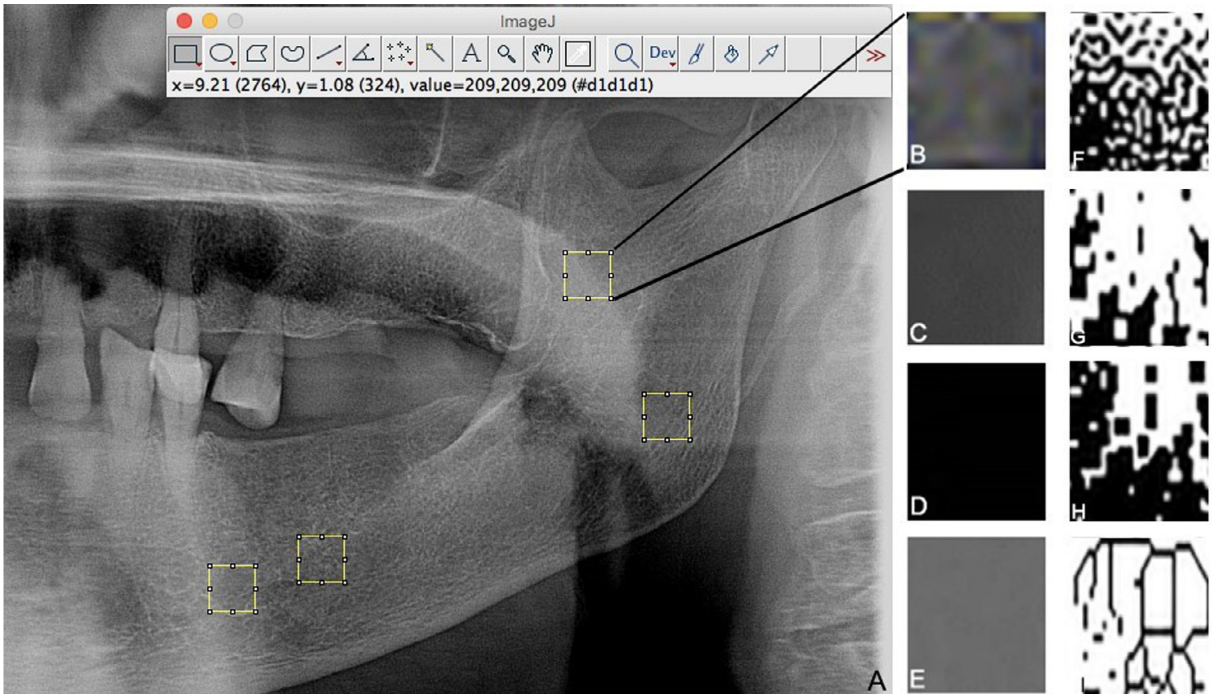

Fig. 5. **(A)** Panoramic radiograph with 4 selected regions of interests. **(B)** Original image. **(C)** Gaussian blurred image. **(D)** Subtraction image. **(E)** Added 128 image. **(F)** Binary image. **(G)** After "erode." **(H)** After "dilate." **(I)** Skeletonization.

- FDs were calculated by using the box-counting method with the help of the software. The mean values of the FDs calculated for the ROIs of 4 different areas of both hemimandibles on each image were transferred to the computer for statistical analysis.

Statistical evaluations were performed by using the Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS Inc., Chicago, IL). To obtain a sufficient case number for this study, a statistician at our university performed sample size determination. The Kolmogorov–Smirnov test was used to analyze all continuous variables to determine whether the distribution provided normality. Data were expressed as mean ± standard deviation. Fisher's exact test and the χ^2 test were conducted for comparison of the measured data from the different groups. Mann-Whitney U test and Student *t* test were used to compare the quantitative variables between group I (without bone exposure) and group II (with bone exposure). Multivariate ordinal logistic regression was performed to determine the radiographic findings that predicted the development of MRONJ. All data were evaluated at a significance level of $P < .05$.

RESULTS

Table I lists the characteristics of the patient populations in groups I and II. There were no significant differences between the 2 groups in age, gender, systemic diseases, or duration of drug therapy. No significant differences were discovered with regard to location or local etiologic factors for necrosis. There were statistically significant differences between groups I and II in the drug type and route of drug administration ($P < .01$). Drugs were mainly used for the treatment of cancer or osteoporosis. The most commonly prescribed drugs were alendronate for patients in group I and zoledronic acid for patients in group II. The mean duration of medication use in group I was 21 months (range 1–4 years), whereas in group II, it was 48 months (range 2–11 years). The most common causative factor for MRONJ in both groups was dental extraction (group I: 21 cases; group II: 27 cases).

Radiographic findings

Focal sclerosis, diffuse sclerosis, sequestrum, and enhancement of the inferior alveolar canal were significantly more prevalent in group II ($P = .036$; $P = .041$; $P = .032$; and $P = .012$, respectively). Other radiographic features did not show any significant differences between the groups (Table II). To express the intensity of the variables, radiographic signs were analyzed according to the number of segments in which they occurred in the whole sample. In this analysis, osteolysis, focal sclerosis, thickening of the lamina dura, and enhancement of the external oblique ridge were the most commonly observed findings. The most common findings in group I patients were osteolysis, lamina dura thickening, and enhancement of the external oblique ridge, which were found in greater numbers

Table II. Occurrence of radiographic signs in group I and group II according to number of segments

Radiographic Signs	Number of Segments (66 × 6 = 396)								P value
	Group I (28 × 6 = 168)				Group II (38 × 6 = 228)				
	Presence		Absence		Presence		Absence		
	n	%	n	%	n	%	n	%	
Osteolysis	32	19.1	136	80.9	54	23.6	174	76.4	0.087
Cortical erosion	6	3.5	162	96.5	22	9.6	206	90.4	0.421
Focal sclerosis	12	7.1	156	92.9	28	12.2	200	87.3	0.036*
Diffuse sclerosis	11	6.5	157	93.5	24	10.5	204	89.5	0.041*
Sequestrum	5	2.9	163	96.9	21	9.2	207	90.8	0.032*
Thickening of lamina dura	14	8.3	154	91.7	29	12.7	199	87.3	0.671
Inferior alveolar canal (Segments 4 and 6)†	3	5.3	53	94.7	26	34.2	50	65.8	0.012*
Persistent alveolar socket	8	4.7	160	95.3	18	7.8	210	92.1	0.222
Pathologic fracture	0	0	28	100	4	1.7	224	98.3	0.103
External oblique ridge (Segment 4 and 6)†	13	23.2	43	76.7	29	38.1	47	61.9	0.686

*$P < 0.05$.
†Segment 4: right posterior mandible; and segment 6: left posterior mandible.

of segments in group II patients. All radiographic findings that showed a higher prevalence in group II occurred more frequently in the mandible than in the maxilla: osteolysis (21.7%), in which segment 4 (38.2%) was the most prevalent; lamina dura thickening (10.8%), in which segment 6 (27.6%) was the most prevalent; and enhancement of the external oblique ridge (31.8%), in which segment 4 (65.9%) was the most prevalent. With regard to the comparison between radiographic findings and route of administration, there was a statistically significant positive correlation between the intravenous route of administration of medication and the prevalence of radiographic findings ($P < .01$). However, the determination of the odds ratio (OR) and its 95% confidence interval (CI) showed an increased risk for developing any of these signs in group I, except the presence of diffuse sclerosis (diffuse sclerosis; OR: 0.4094; 95% CI 1.0004−1.0195; $P = .045$) (Table III). Note that the CIs are wide, considering the small sample size.

FD analysis results

The mean FD values and standard deviation in groups I and II were 1.42 ± 0.11 and 1.44 ± 0.18, respectively. On comparing the FD values of the 2 groups at 4 different regions, patients in group II had higher mean FDs compared with those in group I at regions closer to the alveolar bone, but the differences were significant only in ROI-4 (P = .039). Overall, there was no difference in FD between the groups. Table IV shows the FD values according to the region in group I and group II.

DISCUSSION

The use of bone exposure as a criterion in the diagnosis of MRONJ causes delay in diagnosis and resistance to treatment.[22] Stage 0 is described as an unexposed variant of MRONJ and presents nonspecific clinical findings, radiographic changes, and symptoms. Lack of specific clinical features often causes diagnostic difficulty for clinicians. In such cases, radiologic

Table III. Radiologic findings that correlate with the development of medication-related osteonecrosis of the jaw (MRONJ) based on logistic regression analysis

Variable	Odds ratio	95% confidence interval	P value
Osteolysis	3.6251	0.2436−34.218	.392
Cortical erosion	1.2108	1.0002−1.0187	.269
Focal sclerosis	1.9262	0.7798−10.6138	.147
Diffuse sclerosis	0.4094	1.0004−1.0195	.045*
Sequestrum	0.2148	0.5259−3.8716	.621
Thickening of lamina dura	1.2513	0.36754−3.3125	.124
İnferior alveolar canal	2.4150	0.8945−8.6259	.212
Persistent alveolar sockets	2.1492	0.2543−3.4158	.637
Pathologic fracture	3.8944	1.1707−10.0763	.482
External oblique ridge	1.0625	0.4952−1.7016	.346

*$P < .05$.

Table IV. Fractal dimension values of the four regions of interest (ROIs) on panoramic images of patients in this study

ROI	*n*	*Group*	*FD (mean)*	*SD*	*P value*
ROI-1	28	Group I	1.41	0.032	.124
	38	Group II	1.40	0.044	
ROI-2	28	Group I	1.32	0.046	.348
	38	Group II	1.32	0.045	
ROI-3	28	Group I	1.46	0.040	.091
	38	Group II	1.49	0.048	
ROI-4	28	Group I	1.49	0.036	.039*
	38	Group II	1.56	0.042	

*$P < .05$.
FD, fractal dimension; *ROI,* region of interest; *ROI-1,* cancellous bone anterior to the mandibular foramen; *ROI-2,* above the supracortical area in the angle of the mandible; *ROI-3,* cancellous bone anterior to the mental foramen; *ROI-4,* cancellous bone above the mandibular canal on the distal side of the mental foramen; *SD,* standard deviation.

examination may be useful for correct diagnosis and evaluation of osseous changes.

Some studies have reported concerns with regard to the use of radiography for diagnosing MRONJ.[23-25] However, there is no consensus regarding which imaging technique should be used for the diagnosis, staging, and treatment of MRONJ. Some authors have argued that panoramic radiography may give misleading results because it does not correctly demonstrate the sizes of lesions; thus, advanced imaging methods, such as computed tomography, cone beam computed tomography (CBCT), or magnetic resonance imaging, should be used for this purpose.[26] The most important advantage of these imaging modalities compared with panoramic radiography is that they provide images with better definition. In addition to this, all patients undergoing antiresorptive treatment should initially have a panoramic radiographic examination, with further examinations later, if needed.[27] Our literature review revealed that the studies using CT, CBCT, or magnetic resonance imaging did not include sufficient numbers of stage 0 patients.[28-30] Thus, we believe that the findings of our investigation will be more beneficial to general dental practitioners.

Kubo et al.[31] investigated panoramic radiographic signs that can be used to predict the development of BRONJ. Sclerosis of the trabecular bone and thickening of the lamina dura were more frequently found in the group of patients who had taken BPs (and did or did not have BRONJ) than in the control group. However, these investigators were unable to find any radiographic signs that acted as indicators of BRONJ.

In a case-control study conducted by Klingelhöffer et al.,[13] sclerosis, visible alveolar sockets, enhancement of the lamina dura and mandibular canal, proliferative periostitis, and osteolysis were found to be significantly more frequent in patients treated with antiresorptive drugs than in the control group. In addition, the determination of the OR showed an increased risk for developing only the sign of sclerosis with antiresorptive treatment.

In our study, the most commonly encountered findings in both groups were osteolysis, focal sclerosis, thickening of the lamina dura, and enhancement of the external oblique ridge, corroborating the findings of previous studies.[32,33] In group I (early-stage MRONJ), the most common findings were osteolysis (19.1%), thickening of the lamina dura (8.3%), and enhancement of the external oblique ridge (23.2%). For stages 1, 2, and 3, which are the advanced phases of MRONJ (group II), the most commonly reported findings were osteolysis (23.6%), inferior alveolar canal enhancement (34.2%), and enhancement of the external oblique ridge (38.1%). Even though all of the radiographic findings were seen more often in group II than in the group I, the difference was significant only for focal and diffuse sclerosis, sequestrum, and enhancement of the inferior alveolar canal ($P < .05$). Findings from the present study, in which panoramic radiographs were used for analysis, suggest that diffuse sclerosis may be an indicator of MRONJ development.

The trabecular network of the alveolar bone has a structure that can be characterized by FDs. A higher FD represents complex bone architecture, with denser and less porous trabeculae.[34] The FD analysis method, which is believed to be independent of such variables as projection geometry or radiodensity, can indicate the first signs of changes in the alveolar bone in the early stages of MRONJ.[14] The FD analysis method is used in dentistry for such tasks as evaluation of bone quality in implant regions or the detection of changes in periodontal tissues.[35,36] However, its use in evaluating changes in the jaws in patients with MRONJ has been limited. In these studies, healthy individuals and patients who had received BP treatment formed the two groups. The deficiency in previous research was the absence of grouping based on the AAOMS staging system. To overcome this, the present study classified patients according to the latest staging system (early/advanced).

Torres et al.[18] used CBCT to compare the FDs of patients with BRONJ and a healthy control group. The results revealed higher FD values in the BRONJ group (1.67−1.72) than in the control group (1.65−1.67). Significant differences were present only in the trabecular bone above the mandibular canal. The values in our study were much lower than those reported in the article by Torres et al. (group I: 1.42 and group II: 1.44). FD analysis in the study by Torres et al. was performed by using CBCT, precluding a direct comparison with the results of the present study.

Demiralp et al.[19] measured the FD values on the panoramic radiographs of 33 patients with MRONJ and compared them with those of a control group. Their results showed that the FD values were 1.39 ± 0.14 in the study group and 1.38 ± 0.07 in the control group ($P > .05$). Also, there was no significant difference in the FD values of the tested regions. The results of our study revealed no statistically significant differences between group I and group II ($P > .05$). The patients in group II had higher mean FDs compared with those in group I at regions closer to the alveolar bone, but the differences were significant only in the area of the cancellous bone above the mandibular canal on the distal side of the mental foramen ($P = .039$). The differences between the FD values reported by Demiralp et al. and those of the present study may have been influenced by the discrepancies in the selection of ROIs, sizes of ROIs, and patient differences.

Most previous studies used the FD, panoramic mandibular index, mandibular cortical index, and mandibular cortical width on panoramic radiographs to determine the mandibular cortical and trabecular bone changes in patients with MRONJ.[8,37,38] To our knowledge, this is the first study investigating radiographic changes in the early stage of MRONJ through FD analysis of panoramic radiographs. Therefore, more studies performing FD analysis of the radiographs of patients with MRONJ are needed to compare with the results of the present investigation.

In this study, we examined panoramic radiographs and evaluated the radiologic changes observed in the early and advanced stages of MRONJ with respect to several parameters. The study had the usual limitations of a retrospective investigation with a relatively small sample size. The main limitations of this study are that the panoramic radiographs were not compared with images from different imaging modalities with regard to accuracy and that there was no control group with healthy individuals. We did not analyze the influence of medications on radiographic features.

CONCLUSIONS

The results of this study showed that focal and diffuse sclerosis, sequestrum, and enhancement of the inferior alveolar canal were significantly more prevalent in patients with advanced-stage MRONJ. No significant differences were detected in the FD values among the tested regions except in the area of the cancellous bone above the mandibular canal on the distal side of the mental foramen. If the radiographic features related to the development and early stages of MRONJ could be detected before dental procedures, this knowledge could be used by clinicians to minimize the risk of progression to the severe stages of the disease. Further clinical studies should evaluate the risk of osteonecrosis occurring after surgical treatment or denture-induced trauma when radiographic findings are present in patients with stage 0 MRONJ. In addition, the influence of the medication types, duration, and dosages on FD values and on the prevalence of the radiographic features are interesting topics of future research.

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