Fractal and radiomorphometric analysis of mandibular bone changes in patients undergoing intravenous corticosteroid therapy

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Objective. To evaluate mandibular bone changes by comparing the fractal dimension (FD), mandibular cortical width (MCW), and panoramic mandibular index (PMI) on panoramic radiographs in patients using intravenous corticosteroids versus controls.
Study Design. In total, 60 patients were divided into 2 groups: 30 patients receiving intravenous corticosteroid treatment and 30 age- and sex-matched healthy people as the control group. Panoramic radiographs of all patients were evaluated. FD was measured in 4 regions: the subcortical area in the condyle, the area superior to the angle of the mandible, the alveolar bone distal to the mandibular left second premolar root, and the alveolar bone mesial to the mental foramen. MCW and PMI were calculated to assess cortical thickness.
Results. The FD values in the condyle, angle of the mandible, and mental foramen region were significantly lower in the corticosteroid group ($P \leq .011$), but there was no significant difference in the second premolar area ($P = .101$). MCW values were significantly lower in the corticosteroid group ($P < .001$). There was no significant difference in PMI between the groups ($P = .544$).
Conclusions. The FD and MCW values of the patients using corticosteroids can be helpful in quantitatively and objectively evaluating osseous changes in patients receiving intravenous corticosteroids. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:110−115)

Corticosteroids (CS) have immunosuppressive and anti-inflammatory effects at certain therapeutic doses.[1] For this reason, they are often prescribed in treatment of diseases such as rheumatoid arthritis, vasculitis, systemic lupus erythematosus, polymyalgia rheumatica, inflammatory enteric diseases, and glomerulonephritis.[2] In addition, CS can be used topically or systemically in the treatment of oral diseases such as lichen planus, pemphigus, erythema multiforme, recurrent aphthous stomatitis, and allergic reactions.[3,4] Many side effects on bone metabolism are encountered during CS use.[1] Osteoporosis is a common side effect, whereas avascular necrosis is less likely.[5,6]

In patients with CS-induced osteoporosis, loss of bone mineral density is biphasic; it occurs rapidly (6%−12% loss) in the first year and then slowly (about 3% loss per year).[7] However, the risk of fracture typically increases by up to 75% within the first 3 months after the start of treatment. A significant decrease in bone mineral density may not be captured by bone densitometry.[8]

The effects of CS on bone have been investigated. Toogood et al.[9] reported that CS therapy may adversely affect bone density. Another study stated that bone loss at the femoral neck suggests an increased risk of fracture at that site, especially in older patients on long-term CS therapy.[10] Van Staa et al.[7] indicated that corticosteroids are a powerful factor in vertebral fractures. Contrary to these findings, Lespessailles et al.[11] evaluated hip, wrist, ankle, and vertebral fractures and reported that although corticosteroids cause changes in mineral bone loss and trabecular microarchitecture, they are not the primary factor in bone fracture. However, the effects of CS on the mandible have not been evaluated.

Specific digital methods have been developed that can quantitatively evaluate changes in trabecular bone. One mathematical method used for this purpose is analysis of the fractal dimension (FD). Fractal analysis (FA) is used in the investigation of complex shapes and structural formations, and the result obtained from the analysis is defined as the FD.[12] Many studies in the medical field confirm that FA helps detect early changes in bone.[13]

Radiomorphometric mandibular indices of cortical bone measured on panoramic radiographs, including mandibular cortical width (MCW) and panoramic mandibular index (PMI), are good predictors of osteopenia and osteoporosis. *Bone quality* is a collective term referring to the mechanical properties, architecture (thickness of cortical bone, distribution of the trabecular network),

Statement of Clinical Relevance

Fractal analysis is a mathematical method that enables early detection of changes in microtrabecular structure in bone. In this study, fractal dimension (FD) and mandibular cortical width (MCW) values were found to be significantly lower in patients using corticosteroids. FD, MCW, and panoramic mandibular index calculations can be used to quantitatively evaluate trabeculation changes in mandible.

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and degree of mineralization of the bone matrix, as well as the remodeling properties of bone.[14]

The objectives of the study were to compare the FD values, as measured at 4 sites in the mandible, and the radiomorphometric indices of MCW and PMI in patients using CS versus control patients. The null hypothesis stated that there were no significant differences in these values between the 2 groups of patients. The alternate hypotheses stated that the use of CS reduced the thickness and density of the trabeculae and decreased the radiomorphometric values of the cortical bone.

MATERIALS AND METHODS

This study was approved by in Hatay, Turkey (Decision No. 11), was conducted in accordance with the principles set out in the Declaration of Helsinki. This retrospective study involved examination of panoramic radiographs that were exposed previously for various reasons during dental examination in the dentomaxillofacial radiology department, faculty of dentistry. In all, 300 panoramic radiographs in the radiology archive were reviewed. The panoramic radiographs were evaluated on the basis of the following inclusion criteria: clearly visible mandibular anterior and posterior regions, temporomandibular joints, and mental foramina; and continuous mandibular inferior cortices, with no ghost images that would hinder the analysis of the mandibular bone. Radiographs with poor quality, artifacts, fractures or lesions in the jaws, and signs of temporomandibular joint disorders were excluded, as were radiographs of patients taking medications other than corticosteroids. The CS patients were selected from those who were being treated with intravenous CS for chronic renal failure, rheumatoid arthritis, and systemic lupus erythematosus. In total, 60 patients (range 25−50 years) were recruited for the study: 30 CS patients (17 female, 13 male) who had been receiving intravenous CS for more than 1 year; and 30 healthy people (17 female, 13 male) age and sex matched with the patients, who were taking no medication as the control group.

Panoramic radiographs were exposed with the Vatech PaX-i unit (Vatech Co., Hwaseong, Korea) with exposure parameters of 70 kilovoltage peak (kVp), 10 milliamperes (mA), and 9.7-second exposure time. The image analysis program Image J, Version 1.3 (National Institutes of Health, Bethesda, MD, USA) was used for calculation of FD and the radiomorphometric indices on all radiographs.

Fractal dimension

Based on a study by White and Rudolph,[15] a region of interest (ROI) was selected from each of 4 different sites on the image. These were the subcortical area in the condyle, the supracortical area superior to the angle of the mandible, the alveolar bone distal to the mandibular left second premolar root, and the alveolar bone mesial to the mental foramen (Figure 1). The box-counting method was used to perform FD. First, an 18- × 19-pixel copy of each ROI was obtained from the original radiograph.[16,17] This copy was blurred using a gaussian filter. The new image was subtracted from the original image and a gray value of 128 was added to each pixel position. An image with a minimum intensity value of 128 was created to reflect individual differences in the image, such as trabeculae and marrow gaps. The image was then segmented to a binary (black-and-white) image by using 128 brightness threshold values. The black areas on the image were radiographically representative of the trabecular bone. "Erode" and "dilate" were performed to eliminate noise

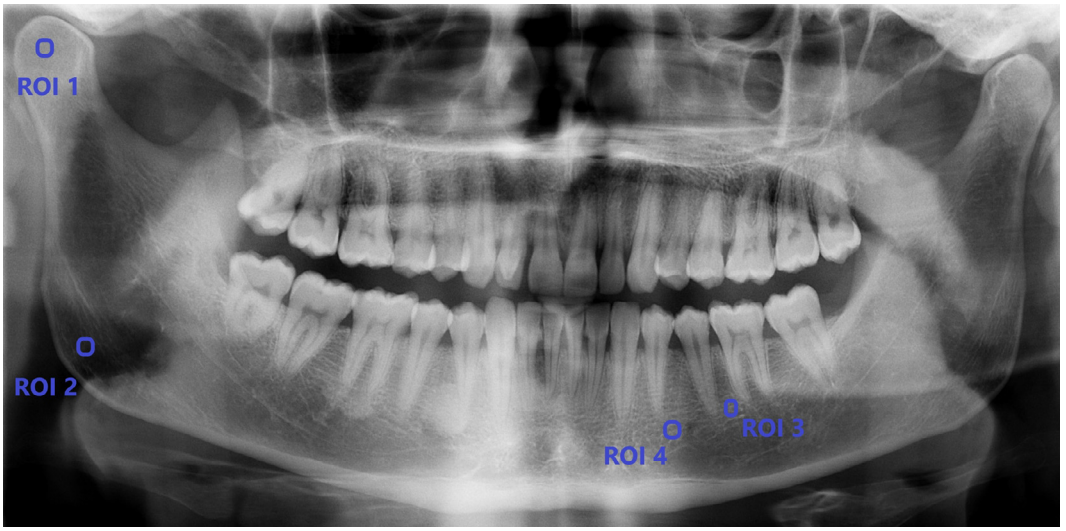

Fig. 1. Regions of interest (ROIs) on panoramic radiographs for fractal dimension analysis. *ROI 1,* Subcortical area in the condyle; *ROI 2,* supracortical area superior to the angle of the mandible; *ROI 3,* alveolar bone distal to the mandibular left second premolar root; *ROI 4:* alveolar bone mesial to the mental foramen.

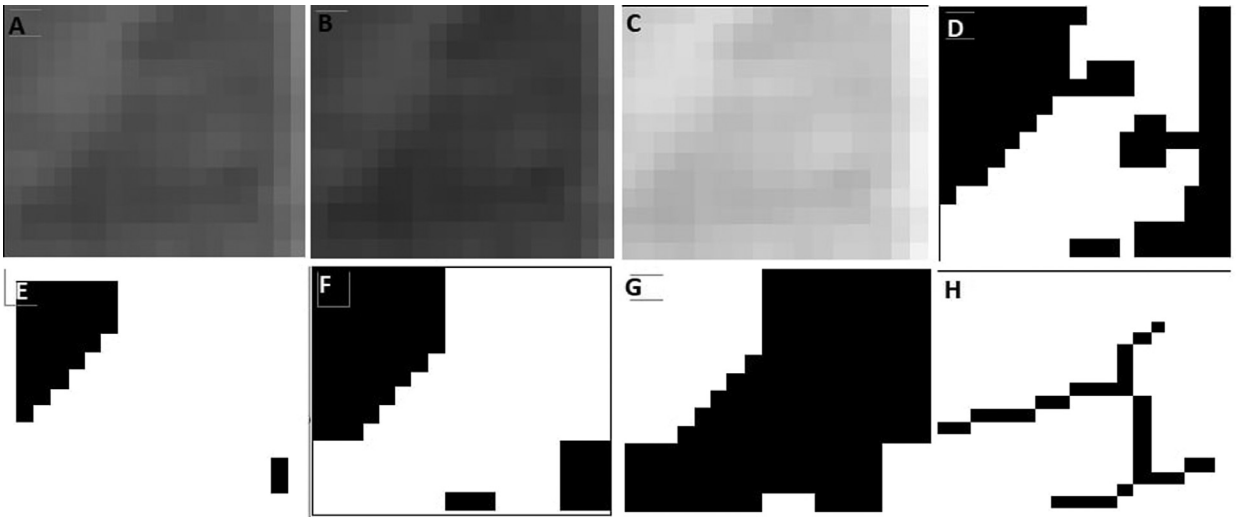

Fig. 2. Fractal analysis procedures. **(A)** Image of the cropped and duplicated region of interest. **(B)** Subtracted image from the original image. **(C)** Addition of a gray value of 128 to each pixel location. **(D)** Binarization. **(E)** Erosion. **(F)** Dilation. **(G)** Inversion. **(H)** Skeletonization.

in the image. After this process, white areas were converted to black and black areas were converted to white by using the "invert" function. "Skeletonize" was performed as the last step in image processing (Figure 2).

Mandibular cortical width

For MCW measurement, a line was drawn tangent to the inferior aspect of the mandibular cortex at the level of mental foramen in the premolar area. A second line was drawn parallel to this line along the superior aspect of the cortex. A third line was drawn through the mental foramen perpendicular to these 2 lines. The distance between the 2 parallel lines at the level of the mental foramen (a) was used to measure mandibular cortical width[14] (Figure 3).

Panoramic mandibular index

In PMI calculation, the distance between the inferior edge of the mental foramen and the inferior border of the mandible was measured (b). The PMI value was calculated by dividing the cortical thickness in the mental region by the distance from the inferior border of the mental foramen to the inferior border of the mandible (a/b)[14] (Figure 3).

All image processing and analysis procedures were performed by 2 dentomaxillofacial radiologists with 6 years (G.S.) and 5 years (C.A.B.) of clinical experience. The FD, MCW, and PMI analyses were performed at the same time. All measurements were made on the same laptop computer (Dell Inc., Round Rock, TX, USA) to rule out changes in image resolution. Image manipulation (magnification, contrast, brightness) was not allowed. The average values of the fractal and radiomorphometric measurements by both observers were used for statistical analysis. Both observers had previously been calibrated for all measurements.

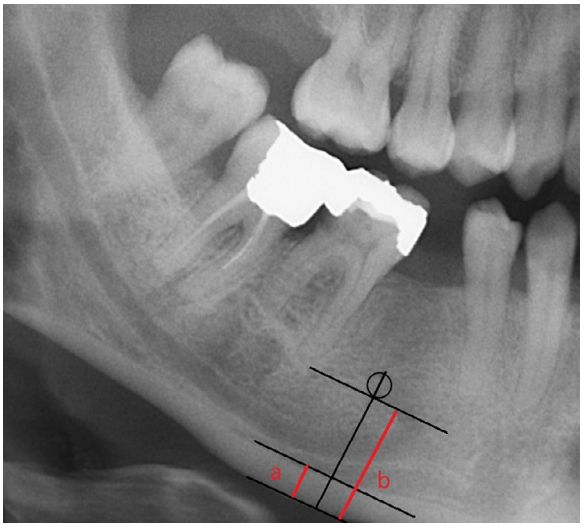

Fig. 3. Measurements of mandibular cortical width (a) and panoramic mandibular index (ratio a/b).

Reliability was evaluated by using repeated measurements. To quantify intraobserver agreement, images of 30 patients (15 CS patients and 15 controls) were randomly selected from the sample and assessed 2 times by the observers at an interval of 1 week after the initial evaluation.

Statistical analysis

The data obtained in this study were analyzed with the Statistical Package for the Social Sciences Version 21.0 (IBM Corp., Armonk, NY, USA). Intraclass correlation values were calculated for interobserver reliability. The conformity of the measured parameters to normal distribution was investigated by the

Table I. Intraclass correlation values of all regions

	Intraclass correlation	*P*
Condyle FD values	0.999	.0001
Angle of the mandible FD values	0.910	.0001
Second premolar FD values	0.996	.0001
Mental foramen FD values	0.980	.0001
MCW (a)	0.977	.0001
(b)	0.955	.0001
PMI (a/b)	0.995	.0001

FD, fractal dimension; MCW (a), mandibular cortical width; (b), distance between the mental foramen and the inferior border of the mandible; PMI (a/b), panoramic mandibular index (ratio a/b).

Kolmogorov-Smirnov test. Because all data were distributed paranormally, the Mann-Whitney *U* test was used for comparisons of FD values between patients and controls at all 4 sites. Data were expressed as mean ± standard deviation. The relationships among FD, MCW, and PMI values were evaluated with the Spearman correlation analysis. The significance level was established at $P < .05$.

RESULTS

The intraclass correlation values indicated excellent reliability for all variables ($P \geq .910$), as listed in Table I. FD values are listed in Table II. The FD values for the CS patients were significantly lower than for the control group in the condyle ($P = .025$) and the angle of the mandible ($P < .001$). There was no significant difference in FD values between the groups in the second premolar area ($P = .101$), but the FD values anterior to the mental foramen were significantly lower in the CS patients ($P = .011$).

The values of the radiomorphometric indices are listed in Table III. The MCW (a) and (b) values were significantly lower in the CS patients ($P < .001$). However, there was no significant difference between the groups in terms of PMI (a/b) ($P = .544$).

DISCUSSION

CS therapy is the most common cause of secondary osteoporosis and the leading iatrogenic cause of the disease. The mechanism of development of osteoporosis is related to an increase in osteoblast and osteocyte apoptosis, which is associated with vascular endothelial growth factor, skeletal angiogenesis, bone interstitial fluid, and decreased bone strength.[8] This may explain how glucocorticoid-induced apoptosis of osteocytes leads to a decrease in bone strength that occurs before loss of bone mineral density.[18] CS therapy also directly reduces osteoclast production but prolong the life of osteoclasts. Therefore, with extended treatment, the number of osteoclasts is usually kept within the normal range, but the number of osteoblasts decreases and bone formation is significantly reduced.[19,20]

CS can cause not only osteoporosis and osteonecrosis but also cataracts and glaucoma, gastrointestinal bleeding, hyperglycemia, hypertension, suppression of growth, menstrual irregularities, resistance to infection, kidney dysfunction, adrenal insufficiency, and steroid withdrawal syndrome.[21] The incidence of osteonecrosis among patients who take CS is estimated to be between 5% and 40%. The risk depends on the dose, duration of therapy, and application of the drug (often intra-articular). Long-term, continuous prednisone therapy has been considered necessary for osteonecrosis development but it has been reported after single, short-course CS therapy.[22]

FA has been used to investigate the effects of some diseases on bone metabolism.[14,23-25] Calculation of FD is a noninvasive procedure that can provide information about trabecular microarchitecture independent of bone density. FA is performed using a computer algorithm. This method is independent of variables such as projection geometry or radiodensity and may be the first predictor of early changes in alveolar bone. Therefore, in cases where the morphometric measurements performed on radiographs are insufficient, FA can detect early changes in the alveolar trabecular bone. FD measurements calculated on images of the jaws obtained with direct digital imaging systems, often using the box counting technique, are a reliable metric for detecting changes in bone

Table II. Fractal dimension values in the 4 regions for the CS patients and control group

								Mann-Whitney U test	
		N	*Mean*	*Median*	*Min*	*Max*	*SD*	*Order average*	*P*
Condyle	Patients	30	0.87	0.89	0.16	1.15	0.21	25.4	.025*
	Control group	30	0.98	1.01	0.67	1.29	0.17	35.6	
Angle of the mandible	Patients	30	0.73	0.75	0.16	1.02	0.21	20.4	<.001*
	Control group	30	0.97	1.03	0.57	1.16	0.16	40.6	
Second premolar	Patients	30	0.89	0.93	0.16	1.07	0.21	26.8	.101
	Control group	30	0.97	1.00	0.63	1.20	0.13	34.2	
Mental foramen	Patients	30	0.73	0.91	0.15	1.05	0.34	24.7	.011*
	Control group	30	0.94	0.97	0.51	1.19	0.16	36.3	

Min, minimum; *max,* maximum; *SD,* standard deviation.
*Statistically significant difference in bold type.

Table III. Radiomorphometric indices for CS patients and control group

		N	*Mean*	*Median*	*Min*	*Max*	*SD*	*Order average*	*P*
MCW (a)	Patients	30	0.60	0.64	0.26	0.88	0.18	40.2	<.001*
	Control group	30	0.38	0.31	0.20	0.73	0.17	20.8	
(b)	Patients	30	2.16	2.27	1.06	2.92	0.52	39.9	<.001*
	Control group	30	1.33	1.05	0.76	2.77	0.63	21.1	
PMI (a/b)	Patients	30	0.285	0.304	0.089	0.404	0.076	31.9	.544
	Control group	30	0.288	0.283	0.207	0.415	0.049	29.1	

CS, corticosteroids; *Min,* Minimum; *Max,* maximum; *SD,* standard deviation; *MCW (a),* mandibular cortical width; *(b),* distance between the inferior border of the mental foramen and the inferior border of the mandible; *PMI,* panoramic mandibular index (ratio a/b).
*Statistically significant difference in bold type.

density.[13,26-28] It appears that although FA has been employed to evaluate osseous changes in the jaws of patients with a variety of disorders affecting bone, no studies have been found regarding FA on the effects of CS on the mandible. Avsever et al.[29] compared the FD values of sickle cell anemia patients and control groups and reported that the FD values in sickle cell anemia patients were significantly lower. Sindeaux et al.[27] discovered that MCW and FD values were significantly smaller in osteoporotic patients compared with healthy patients. Sener et al.[30] used FA to evaluate changes in the trabecular structure of interdental bone between individuals with healthy gingiva or moderate periodontitis. They reported a significant difference in the mean FD values between the 2 groups, indicating that FD values can be used to quantitatively discriminate the trabecular alterations induced by periodontitis. Demiralp et al.[23] applied FA on panoramic images to evaluate the trabecular pattern of patients receiving bisphosphonates as a component of cancer therapy. They selected mandibular ROIs similar to those in the present study and found that the FD values of the patients with cancer were higher than those of the control group, but the differences were not statistically significant. They stated that the reason for the different results in their study was that the ROIs they selected were in different regions in addition to the differences between patient groups. The authors also believed their small sample size might have affected the statistical analysis. Gumussoy et al.[31] discovered that mandibular FD values of patients with chronic renal failure were significantly lower (1.37) than those of the healthy control group (1.41), similar to our findings.

In our investigation, the FD values in the condyle, angle of the mandible, and the site anterior to the mental foramen were significantly lower in patients using CS. The FD values in the second premolar area were also lower in the CS patients, although the difference was not significant. This supports our hypothesis that the trabecular bone of CS-using patients is thinner and less dense.

Although the literature contains no studies comparing MCW and PMI values in patients using CS and healthy individuals, research on the effect of other medical problems affecting the bone, such as breast cancer,[16] thalassemia major,[14] and osteoporosis,[25] on these parameters has been conducted. Göller Bulut et al.[16] reported that FD and MCW values in women with breast cancer undergoing aromatase inhibitor treatment were slightly but not significantly lower than in the control group; PMI was significantly lower. Bayrak et al.[14] reported that MCW was significantly lower in thalassemia major patients than in the healthy control population, but there was no significant difference in PMI between these patients and the control group, similar to our findings. Another study[25] discovered that PMI values were significantly lower in patients with osteoporosis than in the control population. Long-term intravenous corticosteroid use has been reported to cause osteoporotic changes in the mandible.[22] The results of our study, in which MCW measurements were significantly smaller in CS patients than in controls and PMI values were slightly smaller, are generally consistent with these findings. This supports our hypothesis that cortical thickness in the mandible is adversely affected by CS.

One of the limitations of the present study was the small number of patients. We believe that studies with larger numbers of patients in different age groups will contribute more robust data to our knowledge. In addition, the severity of mandibular bone changes in patients taking different doses of CS should be examined. Another limitation was the selection of possibly different-sized ROI areas in measurements made by 2 different observers. To evaluate this, measurements were performed simultaneously by the 2 observers and the results were compared. The agreement between the observers was statistically significant. It has been found that differences in the types of images and spatial resolution resulted in significant variations in the estimates of FD.[32] In this investigation, all measurements were made on the same screen to prevent this problem from affecting the results.

CONCLUSIONS

In the present study we found that FD in some regions and MCW values in patients who had undergone corticosteroid therapy for more than a year were significantly lower than those in the healthy controls. Values of PMI were lower, but the difference between groups was not significant. The side effects of CS on bone metabolism should always be taken into consideration. Patients who require CS over a long period should be examined regularly and bone metabolism should be evaluated.

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