Oral Radiology (2019) 35:23–28
https://doi.org/10.1007/s11282-018-0321-4

ORIGINAL ARTICLE

Trabecular structure designation using fractal analysis technique on panoramic radiographs of patients with bisphosphonate intake: a preliminary study

Kemal Özgür Demiralp[1] · Emine Şebnem Kurşun-Çakmak[1] · Seval Bayrak[2] · Nihat Akbulut[3] · Cemal Atakan[4] · Kaan Orhan[5]

Received: 7 August 2017 / Accepted: 29 December 2017 / Published online: 15 February 2018

Abstract

Objective This study was performed to evaluate the trabecular pattern of patients with cancer taking bisphosphonates on panoramic images using fractal dimension (FD) analysis by comparison with healthy subjects and to assess whether any difference exists between regions.

Methods FD analysis was conducted using ImageJ 1.3 software (National Institutes of Health, Bethesda, MD, USA) with the box-counting method on panoramic radiographs of 33 patients taking bisphosphonates (13 males and 20 females) and 33 healthy sex- and age-matched individuals.

Results FD values were higher (1.39 ± 0.14) in the study group than control group (1.38 ± 0.07) ($p \leq 0.05$). No difference was detected in the FD values among the tested regions. The mean FD values in the control and study groups were as follows: region 1, 1.49 and 1.41 ($p = 0.54$); region 2, 1.36 and 1.37 ($p = 0.84$); region 3, 1.35 and 1.42 ($p = 0.11$); and region 4, 1.39 and 1.39 ($p = 0.90$), respectively. Female patients showed significantly lower values above the mandibular canal on the distal side of the second premolar and anterior to the mental foramen than did male patients ($p \leq 0.05$). Age was unrelated to the FD in the study group ($p \geq 0.05$).

Conclusions The FD values of the patients with cancer taking bisphosphonates were higher than those of the controls. FD analysis showed the potential for examining bone structure in panoramic radiographs. Studies with a larger sample size are necessary to confirm these results.

Keywords Bisphosphonates · Fractals · Panoramic radiography

✉ Seval Bayrak
dtseval@hotmail.com

Kemal Özgür Demiralp
dtkemal.ozgur@gmail.com

1 Türkiye Public Hospitals Agency, Ministry of Health, Cankaya, 06490 Ankara, Turkey

2 Dentomaxillofacial Radiology Department, Dentistry Faculty, Abant İzzet Baysal University, Gölköy Yerleşkesi, Gölköy Kampüsü, Gölköy, 14280 Bolu Merkez, Bolu, Turkey

3 Dentomaxillofacial Surgery Department, Dentistry Faculty, Gaziosmanpasa University, Tasliciftlik yerleskesi, Merkez, 60250 Tokat Merkez, Tokat, Turkey

4 Statistics Department, Faculty of Sciences, Ankara University, Dogol Cad., Besevler, 06100 Yenimahalle, Ankara, Turkey

5 Dentomaxillofacial Radiology Department, Faculty of Dentistry, Ankara University, Besevler 06500, Ankara, Turkey

Introduction

Bisphosphonates are important drugs in many medical fields, especially oncology. They are prescribed for their potential antitumor or antiresorptive functions in managing multiple myeloma, metastatic cancer, and osteoporosis [1, 2].

Bisphosphonate-related osteonecrosis of the jaws (BRONJ) is an important complication that is mostly observed in patients taking bisphosphonates to treat malignant bone metastases and osteoporosis. In 2014, a specific commission of the American Association of Oral and Maxillofacial Surgeons recommended redefining BRONJ as medication-related osteonecrosis of the jaw (MRONJ) [3]. The change is justified to accommodate the increasing number of osteonecrosis cases, including those in the maxilla and mandible, associated with other antiresorptive (denosumab) and antiangiogenic treatments [4].

Normal bone is a dynamic organ that maintains a balance between bone formation by osteoblasts and resorption by osteoclasts. Bisphosphonates decrease bone resorption by inhibiting osteoclasts [2].

Unfortunately, dental radiographs of patients taking bisphosphonates do not allow early diagnosis because of unknown radiological markers. The radiographic findings in patients taking bisphosphonates include osteosclerosis, osteolysis, dense woven bone, a thickened lamina dura, subperiosteal bone deposition, and failure of postsurgical remodeling [5, 6]. In patients with progressive conditions, apparent osseous destruction with mixed radiolucency and radiopacity may be observed in two- and three-dimensional images. Finding early radiological bone changes that indicate the development of MRONJ can help dentists with dental treatment planning and care delivery for patients taking bisphosphonates [1].

Hamada et al. [7] evaluated the early detection of MRONJ using computed tomography (CT) radiodensity values. They found significant differences in cancellous bone radiodensity values between patients with MRONJ with and without necrotic bone, but no significant difference in the cortical bone width was observed. Similarly, Taniguchi et al. [8] reported that the cancellous bone CT values were higher in patients in the bisphosphonate-treated group, who had symptoms, radiological changes, and clinical findings but no clinical evidence of necrotic bone.

Kubo et al. [9] investigated panoramic radiographic features that can be used to predict the development of MRONJ. In patients with osteonecrosis, semilunar defects of the endosteal margin were frequently noted on the affected and contralateral sides, and this feature was determine to be a predictive factor for the development of MRONJ. Sclerosis of the trabecular bone was frequently observed on the affected side in patients with osteonecrosis, and lamina dura thickening was more frequently found in patients taking bisphosphonates than in the control group.

Many published guidelines have provided recommendations regarding the prevention and treatment of MRONJ. In addition, many parameters, data, techniques, and biomarkers have been used to determine the severity or early diagnosis of MRONJ; for example, bone mass density can be measured using dual-energy X-ray absorptiometry scans, and the level of serum carboxy-terminal telopeptide cross-linked type 1 collagen (CTX) can be measured. A blood CTX level of < 150 pg/mL is associated with a high risk of jaw necrosis [10].

Fractal dimension (FD) analysis is a mathematical technique that can aid in quantifying complex structures, including that of the trabecular bone [11, 12]. The structure is characterized by a single number that is calculated by a computer algorithm. The FD is commonly used in nonstandardized radiographs to evaluate and quantify a cancellous bone structure for detecting bone changes, apical healing, periapical bone, and systemic conditions such as osteoporosis. FD analysis uses a box-counting algorithm to quantify the trabecular bone pattern by counting the bone marrow and trabecular bone interface and to access the trabecular and medullar bone boundary. A higher box-counting value is associated with a more complex bone structure [13].

This study was performed to evaluate the trabecular pattern on panoramic images of patients with cancer taking bisphosphonates using FD analysis by comparing their results with those of healthy subjects and to assess whether any difference exists between regions.

Materials and methods

The clinical protocol was approved by the Human Research Local Ethics Committee of the Gaziosmanpasa University Faculty of Medicine. We retrospectively evaluated panoramic radiographs of 33 patients (13 males and 20 females) who took bisphosphonates for treatment of various types of cancer (breast cancer in 15 patients, prostate cancer in 13 patients, and other malignant tumors in 5 patients). The bisphosphonate treatment protocol of all patients involved intravenous administration. Of all 33 patients, 23 used zoledronate and 10 used pamidronate. The mean administration period was 28.2 ± 16.1 months (range 11 months to 5 years).

The radiographs were obtained from the radiology archive of Gaziosmanpasa University, Dentistry Faculty from 2016 to 2017. The control group comprised 33 systemically healthy patients (13 males and 20 females) who were age- and sex-matched with the study group.

All panoramic radiographs were taken using a Morita Veraviewepocs 2D (Kyoto, Japan) at 70 kVp and 10 mA for 9 s. The manufacturer's recommendations were followed while positioning the subjects. Patients who had mandibular pathologies (such as cysts, tumors, or diseases) that might affect bone density (such as osteoporosis, osteopetrosis, or hypo- or hyperparathyroidism) or panoramic radiographs without adequate diagnostic quality were excluded from the study.

FD analysis of each sample was performed using the box-counting method as suggested by White and Rudolph [14]. The images were analyzed using ImageJ version 1.3 software (National Institutes of Health, Bethesda, MD, USA). The periapical and periodontal sites were not used to avoid false interpretation caused by inflammatory alterations.

Regions of interest (ROIs) were selected from four different regions of the left and right mandibles as follows:

- Region 1: subcortical area in the condyle.
- Region 2: above the supracortical area in the angulus mandibulae.

- Region 3: above the mandibular canal on the distal side of the second premolar.
- Region 4: anterior to the mental foramen.

The panoramic radiographs of both groups were converted into tagged image file formats because of their high resolution. Each ROI was selected with the size of 18 × 19 pixels, cropped, and duplicated (Fig. 1). Gaussian blur was used to remove brightness variations due to overlying soft tissues and varying bone thicknesses. The resulting image was then subtracted from the original image. Bone marrow spaces and trabeculae were discriminated from each other by adding a gray value of 128 to each pixel location. After performing binary, erode, dilate, invert, and skeletonize operations, the FD was calculated (Fig. 2).

All measurements were performed by a single dentomaxillofacial radiologist with 10 years of experience in the field. The intraobserver reliability of ROI selection and fractal analysis of the trabecular structure of the four different regions were assessed by re-evaluating ten randomly selected panoramic images twice at a 2-week interval.

SPSS 10.0 software (SPSS Inc., Chicago, IL, USA) was used to store and analyze the data. The level of statistical significance was set at 0.05. An independent-samples *t* test was used to compare the FD values of the control individuals and patient population, and one-way analysis of variance was used to compare subgroups. Pearson's correlation coefficient was used to analyze the correlations between the variables in the patient population.

Results

The systemic intraexaminer error was evaluated at $p < 0.05$ and found to be statistically insignificant. The interclass correlation coefficient measurement indicated good reliability with a mean intraclass correlation coefficient of 0.836 (confidence interval = 0.763–0.887).

The mean age of the study group and control group was 59.8 ± 9.6 years (range 38–78 years) and 61.2 ± 7.2 years (range 41–80 years), respectively. No significant difference was found in the age of the two groups ($p \geq 0.05$). The mean FD values were higher in the study group (1.39 ± 0.14) than in the control group (1.38 ± 0.07) without statistical significance ($p \geq 0.05$). Table 1 shows the FD values according to region in the study group and control group. The FD in the study group was not significantly different between regions as shown by one-way analysis of variance ($p = 0.84$).

Comparison by sex in the study group revealed that for region 3 (on both the right and left sides) and region 4 (on the right side), female patients exhibited significantly lower FD values than their male counterparts ($p \leq 0.05$) (Table 2). Age was found to be unrelated to the FD in the study group ($p = 0.90$). There was no statistically significant correlation between the administration period of bisphosphonates and the FD values ($p = 0.55$).

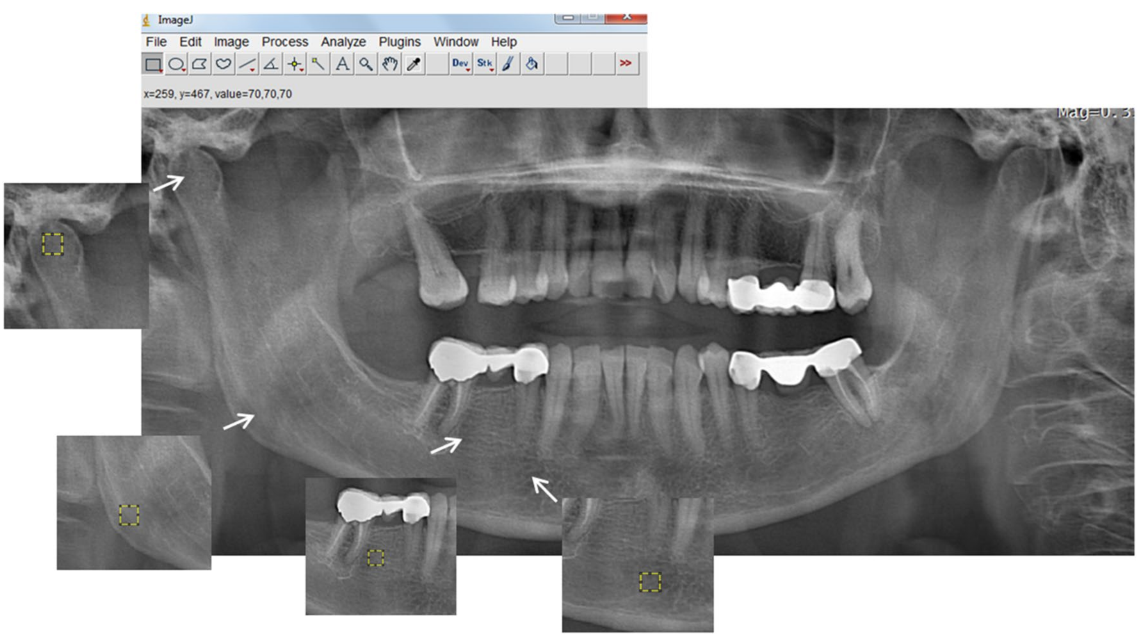

Fig. 1 Panoramic radiograph with four selected regions of interest

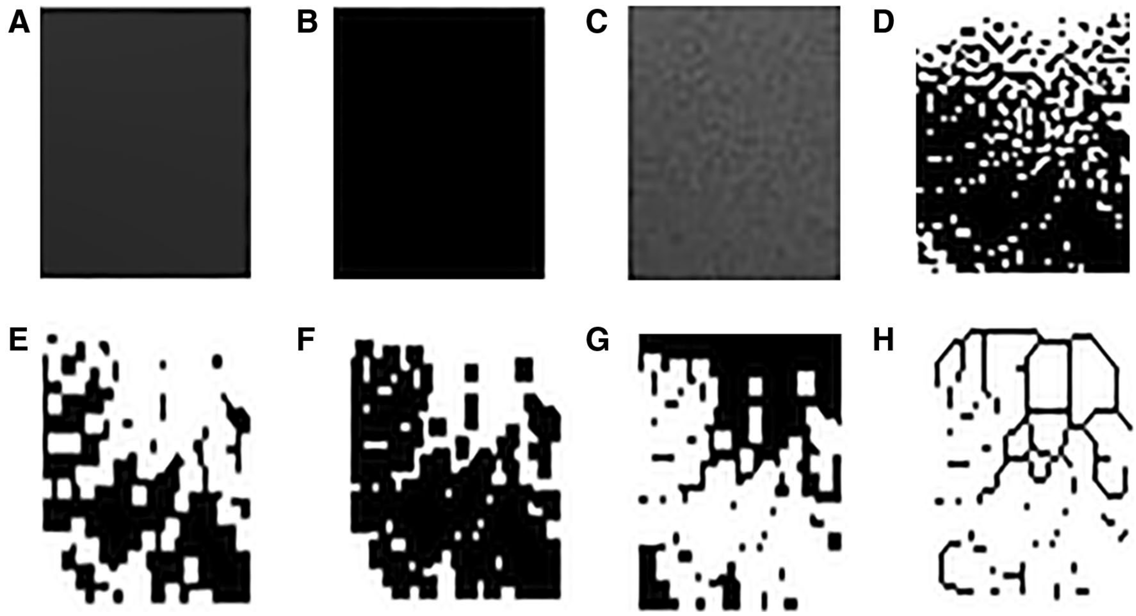

Fig. 2 Stages of fractal dimension analysis. **a** Blurred image of the cropped and duplicated region of interest. **b** Blurred image was then subtracted from the original image. **c** Addition of a gray value of 128 to each pixel location. **d** Binarization. **e** Erosion. **f** Dilatation. **g** Inversion. **h** Skeletonization

Table 1 FD values according to regions in control and study groups

Region	*n*	Group	FD (mean)	SD	SE	*t*	*p* value
1	33	Study	1.41	0.11	0.03	0.60	0.54
	33	Control	1.43	0.18	0.02		
2	33	Study	1.37	0.17	0.02	−0.19	0.84
	33	Control	1.36	0.15	0.02		
3	33	Study	1.42	0.18	0.03	−1.60	0.11
	33	Control	1.35	0.13	0.02		
4	33	Study	1.39	0.15	0.02	−0.11	0.90
	33	Control	1.39	0.14	0.02		

FD fractal dimension, *SD* standard deviation, *SE* standard error

Table 2 FD values and statistical analysis according to sex and side

Side	Region	Female		Male		*t*	*p* value
		FD (mean)	SD	FD (mean)	SD		
Right	1	1.35	0.21	1.44	0.23	−1.13	0.26
	2	1.39	0.15	1.39	0.21	−0.06	0.94
	3	1.35	0.10	1.51	0.23	−2.17	0.03
	4	1.30	0.21	1.55	0.26	−2.64	0.01
Left	1	1.40	0.21	1.47	0.16	−1.08	0.28
	2	1.34	0.21	1.37	0.22	−0.40	0.68
	3	1.36	0.20	1.52	0.17	−2.40	0.02
	4	1.36	0.15	1.41	0.18	−0.90	0.37

FD fractal dimension, *SD* standard deviation

Discussion

Bone quality and quantity measurements have been conducted in the field of dental studies using various techniques such as densitometric and radiomorphometric evaluations [12]. In the 1980s, the concepts of fractal geometry were taken up by many branches of science and entered dental radiography based on an interest in image pattern recognition and medical imaging [15].

Fractal analysis has gained popularity for the detection of potential abnormalities and assessment of the severity of the existing disorders in bone structure. The FD as calculated on two-dimensional radiographs reveals changes in bone architecture and density. A higher FD represents a more complex bone architecture with denser and less porous trabeculae. The method most commonly used in the literature to calculate the FD is box-counting, which was also used in the present study to evaluate the trabecular structure of the mandible [16].

Torres et al. [1] used cone-beam CT (CBCT) to compare the FD between patients with bisphosphonate-associated osteonecrosis and a healthy control group. The results showed higher FD values in the study group (1.67–1.72) than in the control group (1.65–1.67), and a significant difference was present only in the cancellous bone above the mandibular canal. Although no statistically significant difference was detected in the FD values among the regions examined in the present study, the results suggest that the upper area of the mandibular canal distal to the second premolar region, which is the nearest area to the alveolar bone, was the most promising region, because it showed the highest results in the study group and the maximum difference in FD values between the control and study groups. The values in the present study were much lower than those in the study by Torres et al. [1]. The differences in the FD values between their study and ours may have been influenced by the differences in the selected jaw areas and discrepancies in the selection of ROIs. In addition, FD analysis in the study by Torres et al. [1] was performed using CBCT, precluding direct comparison with the results of the present study. Furthermore, the FD can only be reliably compared when using radiographs at the same spatial resolution. CBCT was not chosen in the present study, because it is not a method routinely used in patients who present to a dentist and it delivers considerably more radiation.

Arsan et al. [16] examined the osteoarthritic changes in the trabecular structure of the mandibular condyle in patients with temporomandibular disorders using fractal analysis on panoramic radiographs. The study group exhibited lower FD values (1.22 ± 0.06) than the control group (1.25 ± 0.06). The lower FD value of the study group might have been related to the greater frequency and severity of degenerative changes, because the FD decreased as the severity of degenerative changes increased.

In a study conducted by Gümüssoy et al. [12], panoramic radiographs of patients with chronic renal failure were matched with those of healthy patients. The FD values of the patients with chronic renal failure were significantly lower (1.37) than those of the control subjects (1.41). The researchers detected no sex-related correlation in the FD values. In the present study, female patients exhibited lower FD values in regions 3 and 4.

Demirbaş et al. [17] measured the FD values on panoramic radiographs of 35 patients with sickle cell anemia and compared them with those of a control group, supporting the findings of Gümüssoy et al. [12]. The FD values were found to be lower (1.68 ± 0.08) in the anemia group than in the control group (1.71 ± 0.04). When individuals were subclassified by age (< 20 or ≥ 20 years), the mean FD values of patients aged < 20 years were significantly lower than those of both ≥ 20-year-old patients with sickle cell anemia and all of the healthy controls. In the present study, no significant relationship was detected between age and the FD values of patients taking bisphosphonates.

In the field of periodontics, patients with moderate or severe periodontitis exhibit significantly lower FD values than healthy controls [18]. In endodontics, following successful root canal therapy, FD values showed an increase in the periapical region of intraoral radiographs [19]. Furthermore, Heo et al. [20] reported a gradual increase in the FD during the bony healing process after orthognathic surgery. In another study of implant loading (before-and-after comparison), a significant increase in the FD values was observed after 3 months of implant insertion [21].

The major limitation of this study is the small number of patients included, which might have prevented some associations from reaching statistical significance. Therefore, this study's findings provide only preliminary evidence, and further research is necessary using a larger sample. In addition, the influence of medication procedures (routes, dosages, and types) on FD values may be a topic of future studies.

In conclusion, the results of this study confirmed that fractal analysis has many applications in several branches of dental practice and is a promising economical and readily available method to assess the changes in trabecular bone, as shown by the previous studies. Lower FD values were obtained in healthy subjects than in bisphosphonate users. The most appropriate site of the jaws for evaluating the FD on panoramic radiographs was the region above the mandibular canal on the distal side of the second premolar.

Compliance with ethical standards

Conflict of interest Kemal Özgür Demiralp, Emine Şebnem Kurşun-Çakmak, Seval Bayrak, Nihat Akbulut, Cemal Atakan, and Kaan Orhan declare that they have no conflict of interest.

Human rights statement All procedures followed were in accordance with the ethical standards of the responsible committee (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was not needed in this study.

References

1. 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.
2. 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.
3. 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.
4. Arduino PG, Scully C, Chiusa L, Broccoletti R. Oral squamous cell carcinoma arising in a patient after hematopoietic stem cell transplantation with bisphosphonate-related osteonecrosis of the jaws. Case Rep Dent. 2015;2015:831418.
5. Arce K, Assael LA, Weissman JL, Markiewicz MR. Imaging findings in bisphosphonate-related osteonecrosis of jaws. J Oral Maxillofac Surg. 2009;67:75–84.
6. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res. 2007;22:1479–91.
7. 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.
8. Taniguchi T, Ariji Y, Nozawa M, Naitoh M, Kuroiwa Y, Kurita K, et al. Computed tomographic assessment of early changes of the mandible in bisphosphonate-treated patients. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122:362–72.
9. Kubo R, Ariji Y, Taniguchi T, Nozawa M, Katsumata A, Ariji E. Panoramic radiographic features that predict the development of bisphosphonate-related osteonecrosis of the jaw. Oral Radiol. 2017;1–10. https://doi.org/10.1007/s11282-017-0293-9
10. Friedlander AH, Chang TI, Hazboun RC, Garrett NR. High C-terminal cross-linking telopeptide levels are associated with a minimal risk of osteonecrosis of the jaws in patients taking oral bisphosphonates and having exodontia. J Oral Maxillofac Surg. 2015;73:1735–40.
11. Apolinario AC, Sindeaux R, de Souza Figueiredo PT, Guimaraes AT, Acevedo AC, Castro LC, et al. Dental panoramic indices and fractal dimension measurements in osteogenesis imperfecta children under pamidronate treatment. Dentomaxillofac Radiol. 2016;45:20150400.
12. Gumussoy I, Miloglu O, Cankaya E, Bayrakdar IS. Fractal properties of the trabecular pattern of the mandible in chronic renal failure. Dentomaxillofac Radiol. 2016;45:20150389.
13. de Molon RS, de Paula WN, Spin-Neto R, Verzola MH, Tosoni GM, Lia RC, et al. Correlation of fractal dimension with histomorphometry in maxillary sinus lifting using autogenous bone graft. Braz Dent J. 2015;26:11–8.
14. White SC, Rudolph DJ. Alterations of the trabecular pattern of the jaws in patients with osteoporosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;88:628–35.
15. Zeytinoglu M, Ilhan B, Dundar N, Boyacioglu H. Fractal analysis for the assessment of trabecular peri-implant alveolar bone using panoramic radiographs. Clin Oral Investig. 2015;19:519–24.
16. Arsan B, Kose TE, Cene E, Ozcan I. Assessment of the trabecular structure of mandibular condyles in patients with temporomandibular disorders using fractal analysis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2017;123:382–91.
17. Demirbas AK, Ergun S, Guneri P, Aktener BO, Boyacioglu H. Mandibular bone changes in sickle cell anemia: fractal analysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;106:e41–e8.
18. Updike SX, Nowzari H. Fractal analysis of dental radiographs to detect periodontitis-induced trabecular changes. J Periodontal Res. 2008;43:658–64.
19. Chen SK, Oviir T, Lin CH, Leu LJ, Cho BH, Hollender L. Digital imaging analysis with mathematical morphology and fractal dimension for evaluation of periapical lesions following endodontic treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;100:467–72.
20. Heo MS, Park KS, Lee SS, Choi SC, Koak JY, Heo SJ, et al. Fractal analysis of mandibular bony healing after orthognathic surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;94:763–7.
21. Sansare K, Singh D, Karjodkar F. Changes in the fractal dimension on pre- and post-implant panoramic radiographs. Oral Radiol. 2012;28:15–23.