Mandibular Indexes and Fractal Properties on the Panoramic Radiographs of the Patients Using Aromatase Inhibitors

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Running Title: Radiomorphometric indicies of the Patients Using Aromatase Inhibitors

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Abstract

Objective: This study was conducted to evaluate fractal dimension (FD), mandibular cortical width (MCW), panoramic mandibular index (PMI), and mandibular cortical index (MCI) on panoramic radiographs to determine the mandibular cortical and trabecular bone changes in women with breast cancer undergoing aromatase inhibitors (AIs) treatment .

Methods: In this retrospective study, FD analysis, PMI, MCI, and MCW were assessed over panoramic radiographs of 34 females under AI therapy as a patient group and 34 healthy age-gender matched individuals as a control group.

Results: Mean FD values and MCW were slightly but not significantly lower in the patient group (1.47±0.06 and 4.1±1.2 respectively). FDs measured the supracortical area above the angulus mandibula (FD2) and anterior to the mental foramen (FD4) were significantly lower in patients ($p = 0.037$ and $p = 0.046$ respectively). Among the measured regions in patients; FD2 was significantly lower ($p = 0.001$). PMI was also significantly lower in patients ($p = 0.001$) and MCI were similar in both groups ($p = 0.604$).

Conclusions: AI use affects bone quality and evaluating FD, PMI, and MCW in panoramic radiography can be used to determine the effect of this drug on the jaw bones in the early period.

Advances in Knowledge: Aromatase inhibitors are the most commonly used drugs in breast cancer patients. This drug is thought to have osteoporotic effects on the jawbone. This study is the first study to evaluate osteoporotic changes with measurements made on panoramic radiographs and the results of the study are significant. We think this study will shed light on the studies that will investigate the effects of the drug on the jaw bones.

Keywords: aromatase inhibitors, fractal dimensions, mandibular indexes, osteoporosis, PMI.

Introduction

Breast cancer (BC) is one of the major health problems today, one in every eight women struggles with this disease. [1] It has been known for a long time that nearly one-third of all BCs are estrogen dependent and will decline after estrogen deficiency.[1, 2] Decreasing the effects of estrogen can be mediated by mediators that block estrogen at the receptor level, for example, tamoxifen, or by inhibitors of oestrogen biosynthesis, as the aromatase inhibitors (AIs).[1, 3] The third generation AIs letrozole, anastrozole, and exemestane are the preferred agent in these patient groups. [4-6] Side effects of AIs result from rapid decreases in circulating estrogen.[7] The main adverse effects of AIs causing the depletion of estrogen in women are associated with reduction of bone mineral density (BMD), skeletal and alveolar bone loss resulting in osteopenia, osteoporosis, and fractures, and joint symptoms in woman.[4, 5, 8, 9]

Osteoporosis is a progressive systemic skeletal disease, causing increased fracture risk and bone fragility, characterized by osteopenia (low bone mass) and micro architectural corruption of bone tissue. [10] Various methods can be used to measure bone mass like dual-energy x-ray absorptiometry (DEXA), digital X-ray radiogrammetry, quantitative ultrasound (QUS), quantitative computed tomography (QCT), and other radiographic techniques. [10, 11] The most accepted method is DEXA for assessing bone mineral density (BMD), but it has high cost and limited availability in routine use. Radiographs and image processing techniques have been developed to allow the quantification of mandibular bone mass and trabecular microarchitecture to predict low BMD of the skeletal system in patients.[12-15] The efficiency of the panoramic radiograph in identifying mandibular osteoporosis was shown in different populations.[4] Mandibular indices measured on panoramic radiographs are good predictors of osteopenia/osteoporosis.[5] Fractal dimension (FD) analysis is another technique that has been used to measure mandibular bone mass and trabecular architecture. This is a mathematical technique that can help to digitize complex structures.[12] In this method, a mathematical and morphological image processing system has been used to perform FD analysis. [16] Fractal analysis and mandibular indexes are parameters that can be measured in existing panoramic images of patients and do not require an extra imaging and material need.

Hence this study was undertaken to estimate the bone quality and quantity of patients under AIs therapy by FD analysis and assessment of panoramic mandibular index (PMI), mandibular cortical width (MCW), and mandibular cortical index (MCI) on dental panoramic radiographs.

Materials and Methods

The Research Ethics Committee of the University approved this study (Decision no:2017/195). Panoramic radiographs of women who had previously applied for dental treatment in the Faculty of Dentistry, Department of Dentomaxillofacial Radiology were used to obtain the data of the present study. To be included in the study, the women should have dental panoramic radiographs performed that meet the technical quality criteria and the mandibular cortical bone and borders must be completely visible. Images of patients without periapical pathology in the teeth adjacent to the areas where fractal dimension measurement was to be performed were included. Women with diseases such as diabetes, osteoporosis or hypo- or hyperparathyroidism that affect bone density, temporomandibular joints diseases that can affect the subcondylar area and who have mandibular pathologies such as cystic tumors or who have panoramic radiographs with inadequate diagnostic quality are excluded from the study.

The study consisted of two different groups; patient group: women using AIs for more than 2 years and, control group; gender- and age-matched healthy women for each BC patients. The final sample consisted of panoramic radiographs of 68 selected women (34 women under AIs treatment and 34 for the control group) from the same archives. All radiographs were taken using the same panoramic machine Soredex (Cranex Novus, Tuusula, Finland at 70 kVp, 10 mA for 8 s exposure time.). The patients positioned so that the Frankfurt plane parallel to the floor and the sagittal plane to be parallel to the vertical plane of the dental panoramic machine.

Measurement;

The images were analyzed using ImageJ version 1.3 software (National Institutes of Health, Bethesda, MD, USA) at a correction for 30% magnification, relatively, to better simulate the clinical situation.

- FD analysis of each sample was performed using the box-counting proposed method by White and Rudolph. [17] Regions of interest (ROI) from four different regions of the right and left mandibles were selected as follows:

ROI 1: the subcortical area in the condyle.

ROI 2: the supracortical area above the angulus mandible.

ROI 3: above the mandibular canal distal side to the second premolar.

ROI 4: anterior to the mental foramen (Fig. 1).

Both sets of panoramic radiographs were converted to tagged image file formats due to their high resolution. Each ROI was selected in an 18 x 19 pixel size, cropped, and duplicated. Gaussian Blur was used to remove the brightness changes depending on the upper soft tissues and varying bone thicknesses. The resulting image was then removed from the original image. Bone marrow cavities and trabeculae were separated from each other by adding 128 gray values to each pixel location. FD is calculated after performing binary, erode, dilate, invert and skeletonize operations (Fig. 2).

- MCW was measured by the vertical line drawn to the interior mandible from the middle of mental foramen (Fig. 3a).

- PMI was the ratio of MCW to the distance between inferior border of mental foramen and inferior mandibular cortex (Fig. 3a).

PMI and MCW were measured separately on the right and left mandibular sides and their means were calculated.

- MCI; the state of the underlying cortical bone of the mandible behind the mental foramen on the left and right sides. It consists of three classes based on the classification of Klemetti et al.[18]: C1 = normal cortex: The endosteal margin of the cortex is matched and tapered on both sides; C2 = moderately worn cortex: endosteal margin, lacunar resorption resulting in semilunar defects or formation of endosteal cortical residues; C3 = Over-eroded or porous cortex: forms dense layers of cortex, endosteal and clearly porous cortical remnants (Fig. 3 b, c).

One dentomaxillofacial radiologist with 10 years of experience was carried out all the measurements independently. The FD, MCW, PMI and, MCI analyses were performed at the same time. To assess the intra-examiner calibration of ROI selection, measurements and fractal analysis of the trabecular structure of the four different regions were assessed by re-evaluating randomly selected 20% CBCT images again 2 weeks later.

Statistical analyses

Statistical analyses were conducted with SPSS for Windows SPSS® v. 16.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). The intra-observer correlation coefficient was 0.94 for all assessment. The measurements were evaluated using the independent samples t-test to compare the means of all values between patients and controls. Repeated measurement analysis of variance was used to compare subclasses. Pearson chi-square analysis was used to analyse the correlations between the variables in the groups. $P<0.05$ values were considered to define statistical significance.

Results

Descriptive values of the measurements made in the patient and control group were given in table 1. When the table was observed, it was found that the mean of FD2 and FD4 was significantly higher in controls ($p = 0.037$ and $p = 0.046$ respectively) than in patients, but the mean FD values obtained by averaging the FD values of 4 different regions were not significantly different between the two groups. Mean FD1, FD3 and mean FD values obtained by averaging the FD values of 4 different regions and MCW were slightly but not significantly higher in the control group. Also, the mean PMI was significantly higher in controls ($p = 0.001$). No significant difference was found between patient and control subjects in other measurements.

The FD values measured from 4 different sites in two groups were compared, there was no significant difference between FD1, FD2, FD3, and FD4 in the control group ($p = 0.088$), but in the patient group; FD2 was significantly lower than in the other 3 regions ($p = 0.001$). However, no significant difference was found between the other 3 regions. Distribution of the results of MCI to groups was shown in table 2. It was determined that MCI were similar in both groups ($p = 0.604$).

Discussion

BC is the most common malignancy among women in the world. It is responsible for 25% of all cancers in women in Turkey and more common in postmenopausal women and around the age of 61 years.[19, 20] AIs have become a standard practice in early-stage BC patients in the postmenopausal period because they reduce the recurrence rate of the disease. For this reason, tens of thousands of women use these drugs so knowledge of potential side effects of AIs therapies is important.[4] Most of the dental complications are seen due to the

anti-estrogen effect of AIs. They decrease levels of circulating estrogen in postmenopausal women by blocking the action of the aromatase enzyme, which converts androgens to estrogens. One task of estrogen is to inhibit bone resorption cytokines such as IL-1, TNF-a, and IL-6. However, since estrogen deficiency is seen in AI-using patients, it is thought that bone loss may be advanced according to patients who do not use this drug.[3, 21]

In their pilot study, Taichman et al.[33] have shown that AIs use resulted in increased gingival bleeding and periodontitis risk. Previous studies [4, 22] have shown that estrogen level changes alveolar bone density in postmenopausal women. Din et al. [22] and Yasar Bilge et al. [5] stated that; the main side effects of AIs are decreasing of bone mineral density causing osteoporosis, osteopenia, and fractures in a woman. It is estimated that AI-related skeletal bone loss is between 3.9% and 4.1% in the first two years of treatment. [7] Therefore, the hypothesis that AI use increases alveolar bone loss in postmenopausal age due to estrogen insufficiency is a logical hypothesis. [3, 4]

As far as we know, our study is the first study to analyse fractal dimensions and measure radiomorphometric indexes on panoramic radiographs in patients using AIs. Fractal geometric evaluation has been used in various fields of science as well as in various studies in order to evaluate the trabecular structure of the bone in dentistry. [12, 15, 16, 23-26] The bone micro-architecture is impaired in patients with osteoporosis of the bone due to various causes (diabetes, osteoporosis, sickle cell anaemia, etc.); the number and the thickness of trabecular bone are reduced, and the distance between the trabeculae is greater. Thus, changes in the bone micro-architecture resulting from osteoporosis change the intensity and texture of the image by altering the weakness of the X-ray. For this reason, fractal geometric applications and FD can be used to describe the complex structure of the trabecular bone. [16] The FD calculated on two-dimensional radiographs gives a change in the bone structure such as thickening and resorption in trabeculae and changes in density. [25] The high FD value indicates that the bone is more complex and dense, whereas the lower FD indicates that the bone is more porous.[27 28] The measurement of FD is easy and the region to be measured is determined subjectively. The most commonly used method for FD measurement is the box-counting method and we used this method in the present study.[25, 27]

In Demiralp et al.'s study on panoramic radiography, it was indicated that the FD findings were higher in patients using bisphosphonates, and the cause of the findings was linked to the decrease in bone resorption in these patients. [25] In studies done with panoramic

radiography; Demirbas et al [28] found that patients with sickle cell anaemia had lower FD. Similarly, Gumussoy et al.[16] found that FD was lower in patients with chronic renal failure than in the control group. In the study of Updike et al.,[29] FD was found to be lower in patients with moderate to severe periodontitis and in another study conducted by Chen et al., [30] FD increased in the periapical tissue healing after endodontic treatment. In the present study, the mean FD was lower in patients using AI and FD measured in the supracortical area above the angulus mandible and anterior to the mental foramen was significantly lower in these patients. This confirms our hypothesis that the trabecular bone of AI-using patients is thinner and less dense.

Likewise, there are several studies evaluating the correlation between panoramic radiograph and BMD. [12, 13, 16, 18, 25, 26, 31] Bone quality and quantity was assessed by measurements such as MCW, MCI and PMI measured from specific locations on the panoramic radiographs. [10, 13, 32-36] Panoramic radiography was used in our study because it was taken more frequently in the patient examination and was an easily applicable method. The results of the several studies in the literature show that patients with osteoporosis present lower MCW values. [13, 16, 17, 24, 33, 37-39] Some authors [12, 13, 23, 31] evaluated MCI in these patients with lower MCW and found an association between MCI and MCW. The study by Gulsahi et al.[40] found that MCW and MCI had sufficient diagnostic efficacy in osteoporotic patients, but PMI could not be used to assess osteoporosis. Whereas in some studies,[32, 41] MCI was found insignificant in the comparison of osteoporosis and healthy groups similar with the present study but we found PMI and MCW lower in the group using AIs than the healthy controls as expectedly.

There are so many drugs used for the treatment of any disease and affect the bone metabolism as a side effect. AI is one of these drugs, and most of the BC patients use it. Knowing the effectiveness of these drugs on the jawbone during treatment is an important guide in the treatment plan for dentists. The osteoporotic effect is necessary to determine in the early period and panoramic radiography is the most economical and easily applicable imaging technique. As shown in the studies and in the present study, the PMI, MCW and the FD of the trabecular bone are parameters that can be used to determine bone quality and quantity. The main limitation of our study is the small number of patients. It is possible to obtain more stable results with more patients and a study to be done by forming a patient group according to the type, dose, and duration of use of the drug.

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Figure Legends:

Fig.1 Regions of interest on panoramic radiographs for fractal dimension analysis.

Fig.2 Steps of fractal dimension analysis. (a) Blurred image of the cropped and duplicated region of interest. (b) Subtracted Blurred image 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.

Fig.3 (a) Measurements of mandibular cortical width (red line a). Panoramic mandibular index (ratio of A/B). (b) mandibular cortical index C1. (c) mandibular cortical index C2.

Figure 1

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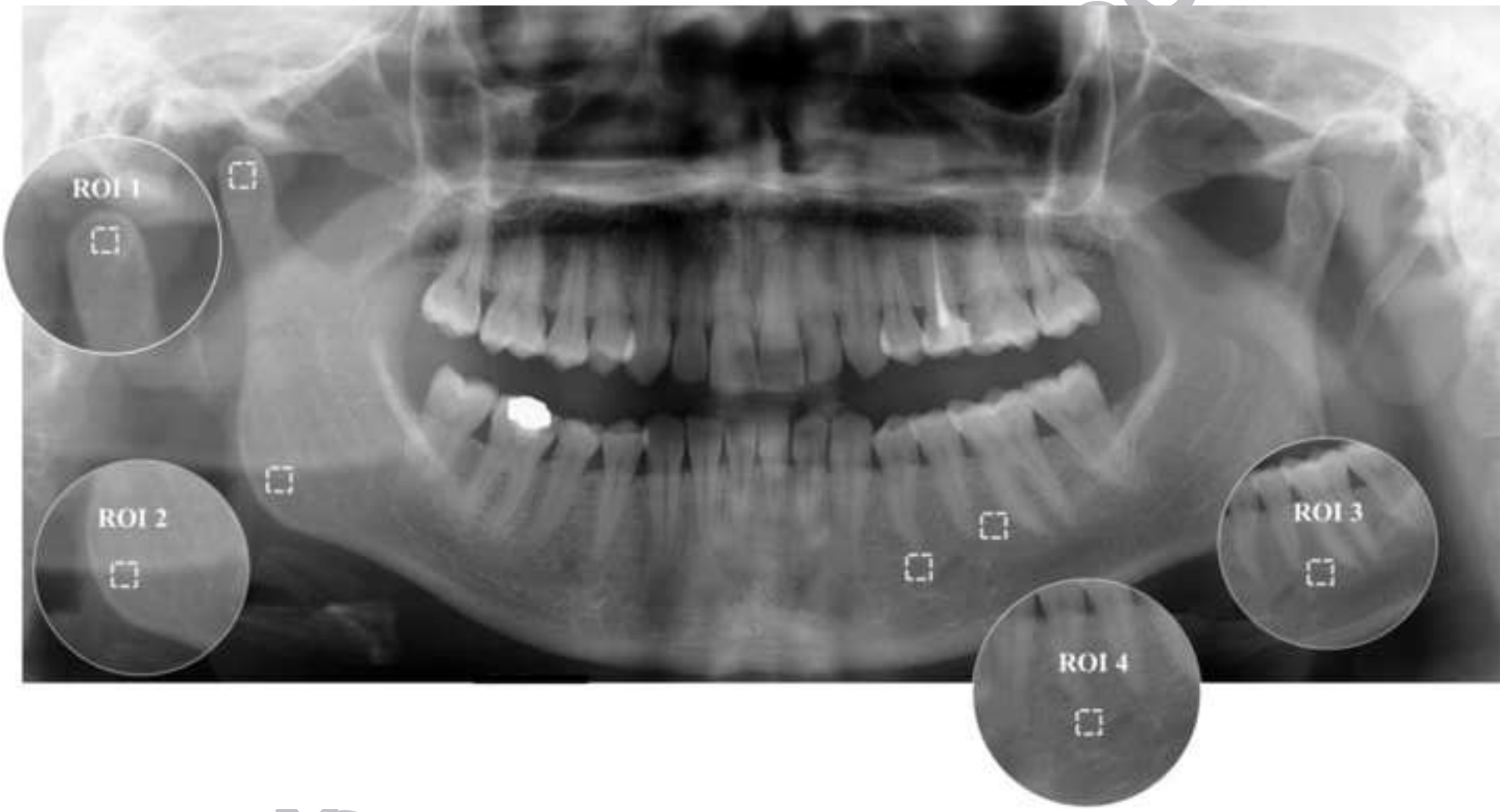

Figure 2

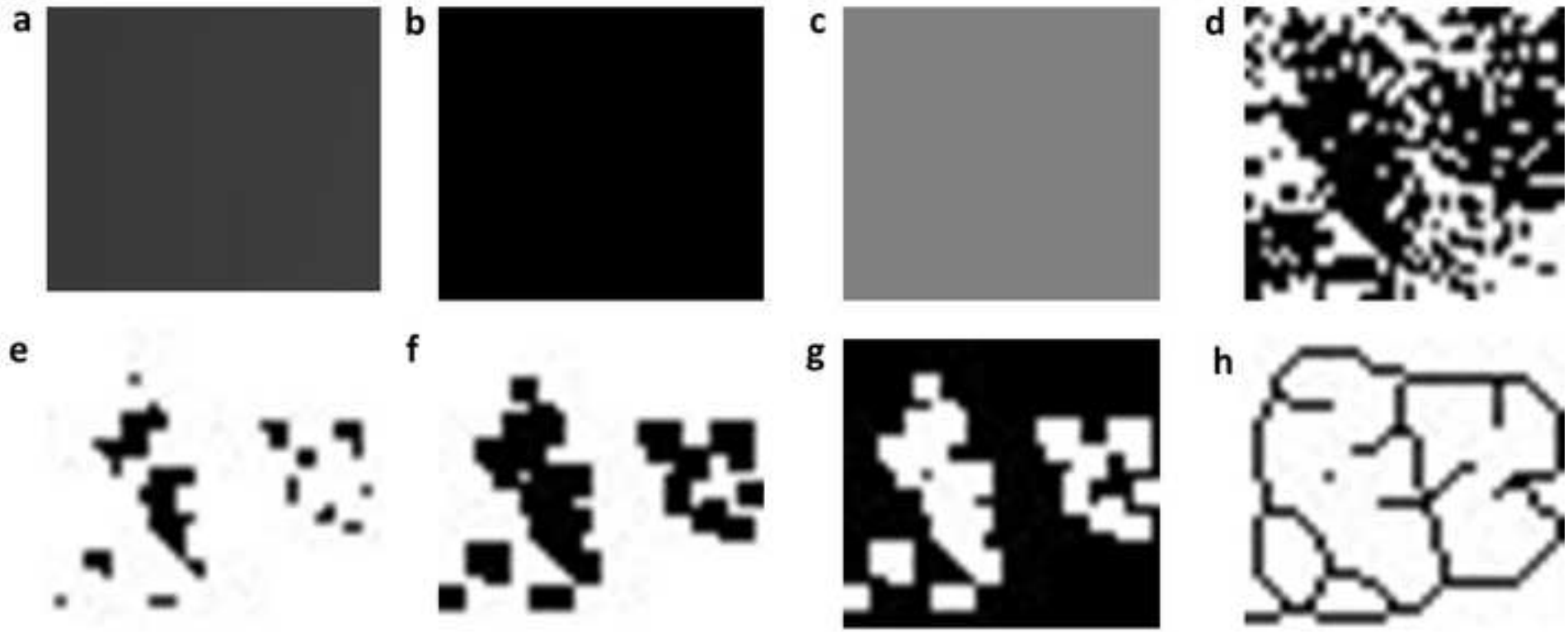

Figure 3

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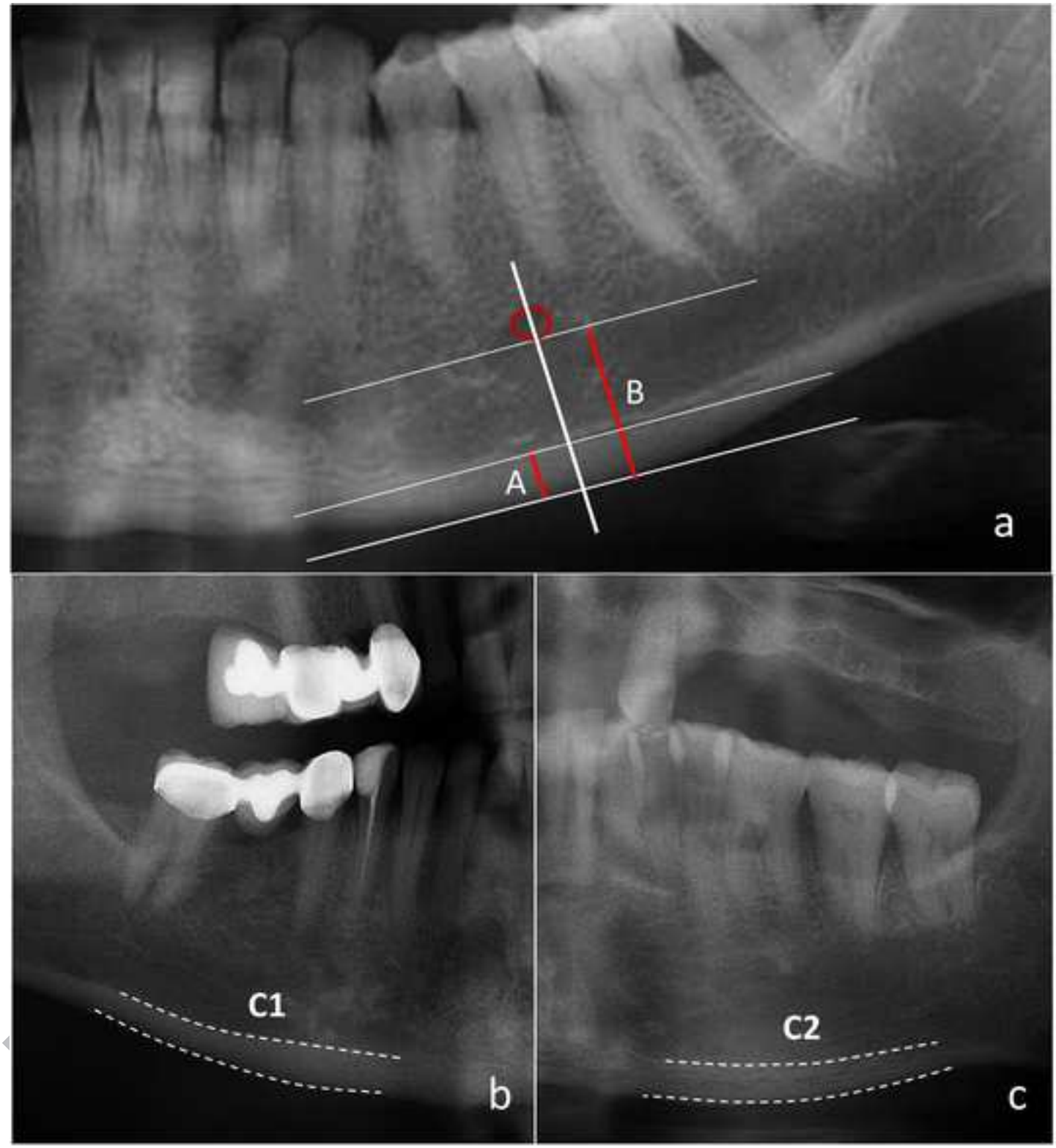

Table 1. Descriptive values of measurements in patient and control group

	Control					Patient					
	N	Mean	SD	Minimum	Maximum	N	Mean	SD	Minimum	Maximum	P value
age	34	63.47	7.46	53	75	34	63.47	7.46	53	75	1.000
FD1	34	1.48	0.11	1.21	1.68	34	1.48	0.12	1.22	1.67	0.791
FD2	34	1.46	0.1	1.23	1.66	34	1.41	0.12	1.21	1.62	**0.037**
FD3	34	1.53	0.11	1.32	1.74	34	1.51	0.1	1.31	1.73	0.354
FD4	34	1.51	0.09	1.28	1.69	34	1.47	0.06	1.41	1.7	**0.046**
mean FD	34	1.49	0.05	1.4	1.59	34	1.47	0.06	1.35	1.6	0.397
PMI	34	0.48	0.09	0.23	0.57	34	0.4	0.06	0.32	0.58	**0.001**
MCW	34	4.64	1.2	2.4	6.3	34	4.12	1.24	1.8	6.3	0.090

FD fractal dimension. SD standard deviation. N number.

Table 2. Distribution of the MCI according to groups.

		Control		Patient	
		N	%	N	%
MCI	1	22	64,7	24	70,6
	2	12	35,3	10	29,4
Total		34	100	34	100

MCI mandibular cortical index, N number.