

Fractal dimension analysis on CBCT scans for detecting low bone mineral density in postmenopausal women

Bruno Fontenele Carvalho¹, Julia Gonçalves Koehne de Castro¹, Nilce Santos de Melo¹, Paulo Tadeu de Souza Figueiredo², Carla Ruffeil Moreira-Mesquita², Ana Patrícia de Paula¹, Rafael Sindeaux³, André Ferreira Leite^{2,*}

¹Faculty of Health Sciences, University of Brasília, Brasília, Brazil

²Division of Oral Radiology, Department of Dentistry, Faculty of Health Sciences, University of Brasília, Brasília, Brazil

³Department of Dentistry, Faculty of Health Sciences, University of Brasília, Brasília, Brazil

ABSTRACT

Purpose: The aim of this study was to compare the fractal dimension (FD) measured at 2 bone sites (second cervical vertebra and mandible) on cone-beam computed tomography (CBCT). The research question was whether FD could serve as an accessory tool to refer postmenopausal women for densitometric analysis. Therefore, the reliability and accuracy of FD were evaluated.

Materials and Methods: In total, 103 postmenopausal women were evaluated, of whom 52 had normal bone mineral density and 51 had osteoporosis, according to dual X-ray absorptiometry of the lumbar spine and hip. On the CBCT scans, 2 regions of interest were selected for FD analysis: 1 at the second cervical vertebra and 1 located at the mandible. The correlations between both measurements, intra- and inter-observer agreement, and the accuracy of the measurements were calculated. A *P* value less than 0.05 was considered to indicate statistical significance for all tests.

Results: The mean FD values were significantly lower at the mandibular region of interest in osteoporotic patients than in individuals with normal bone mineral density. The areas under the curve were 0.644 (*P*=0.008) and 0.531 (*P*=0.720) for the mandibular and vertebral sites, respectively.

Conclusion: FD at the vertebral site could not be used as an adjuvant tool to refer women for osteoporosis investigation. Although FD differed between women with normal BMD and osteoporosis at the mandibular site, it demonstrated low accuracy and reliability. (*Imaging Sci Dent* 2022; 52: 53-60)

KEY WORDS: Osteoporosis; Cone-Beam Computed Tomography; Fractals; Dual-Energy X-ray Absorptiometry

Introduction

Osteoporosis is a common skeletal disease characterized by compromised bone strength that predisposes individuals to fractures caused by minimal trauma, also known as fragility fractures. There are 2 main properties that relate to bone strength: bone mineral density (BMD) and bone

quality.¹ Osteoporosis is a major public health concern due to the social and economic burden caused by fragility fractures. This disease mostly affects the elderly population and postmenopausal women. The costs associated with this disease have tended to rise with population aging.^{2,3} Hence, it is very important to identify low-BMD individuals, especially those who are at a higher risk of fractures.⁴

The diagnosis of osteoporosis is generally based on the measurement of BMD, which is routinely determined by dual-energy X-ray absorptiometry (DXA). Even though DXA is considered to be the gold-standard method for the diagnosis of osteoporosis, the examination is not widely available and its effectiveness is limited when evaluating

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*Correspondence to : Prof. André Ferreira Leite

Division of Oral Radiology, Department of Dentistry, Faculty of Health Sciences, University of Brasília, Campus Universitário Darcy Ribeiro, Asa Norte, Brasília 70910-900, Brazil

Tel) 55-61-31071802, E-mail) andreleite@unb.br

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altered bone quality.^{4,5} Many patients with normal BMD or osteopenia, as defined based on DXA, suffer from fragility fractures.⁶ Therefore, auxiliary methods are necessary to identify microstructural bony changes.

One of the most important factors contributing to bone strength is its complex structure.⁷ Some authors have stated that texture analysis and gray values of radiographic images may be related to bone microarchitecture.^{8,9} Bone texture imaging parameters, including fractal dimension (FD) analysis of the femur and the vertebrae, may improve failure load prediction when added to BMD.¹⁰⁻¹² FD is a mathematical technique that allows complex structures to be quantified in a manner unlike that conducted using conventional mathematical methods. This technique evaluates the level of irregularities and forms of objects. Its value is directly proportional to the image complexity.¹³ Although several studies have tested FD in dental imaging modalities as a complementary tool to identify low-BMD individuals, most of the studies were based on 2-dimensional examinations.¹⁴⁻¹⁹

Cone-beam computed tomography (CBCT) scans have become more popular in dental practice. The elderly population represents the highest-risk group for osteoporosis, and CBCT scans are often used for several reasons in these patients, mainly for planning implants, detecting sites with pathology, and locating retained teeth.^{20,21} Few up-to-date studies have assessed CBCT indices and they have indicated the possibility of osteoporosis screening based on this imaging modality.²²⁻²⁵ Only 2 recent studies have tested FD analysis on CBCT for identifying postmenopausal women with osteoporosis, and those studies reported discordant results.^{26,27} Nevertheless, these studies were substantially different in terms of methodology, had small samples, and were only observational, which means that accuracy measurements were not established for the FD method.

The purpose of this study was to determine whether there were differences in mandibular and vertebral FD analyses on CBCT scans of postmenopausal women with normal BMD and osteoporosis.

Materials and Methods

Initially, 150 patients with normal BMD or osteoporosis were selected from the database of the Bone Densitometry Service of the University Hospital of Brasilia. Of these patients, 103 were included in this study, since 47 were excluded because they had been diagnosed with osteopenia. This exclusion criterion was chosen to avoid middle-range results between normal BMD and osteoporosis. Out of the selected

patients, 52 had normal BMD and 51 were diagnosed with osteoporosis according to lumbar and hip bone density by DXA. The participants were required to be postmenopausal women, aged over 45 years, for whom CBCT exams were indicated for implant planning purposes. Patients who were previously diagnosed with other metabolic bone diseases or had taken medications affecting bone metabolism were excluded. The sample was conveniently composed of partially or totally edentulous postmenopausal women, all of whom had indications for CBCT exams. DXA and CBCT were performed in a similar period, with a maximum difference of 3 months between the exams. The study was approved by the local Institutional Review Board in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All participants included in the study received and signed an informed consent form. The sample size had sufficient statistical power with a distribution t and F equivalent to 0.99 (effect size = 0.3 and type I error = 0.05).

BMD assessment

DXA of the lumbar spine (L1-L4) and hip were performed by the same operator using a Lunar DPX NT device (GE Healthcare, Madison, WI, USA). BMD values for the lumbar spine, femoral neck (FN), and total hip (TH) were classified as normal (T-score ≥ -1.0) and osteoporosis (T-score ≤ -2.5), according to the World Health Organization criteria,²⁸ and the patients were diagnosed with osteoporosis if any of the above-mentioned regions had a compatible T-score. The coefficients of variation of the selected lumbar spine and hip measurements were 1% and 1.2%, respectively.

CBCT scans

CBCT scans were acquired using an I-CAT Classic device (Imaging Sciences International, Inc., Hatfield, PA, USA) with the following parameters: voxel size of 0.25 mm, 120 kVp, 8 mA, field of view of 20 cm \times 8 cm, and a scan time of 40 s.

The images were initially assessed using the software supplied by the CBCT manufacturer (Xoran 3.1.62, Xoran Technologies, Ann Arbor, MI, USA). From all CBCT scans, 2 regions of interest (ROIs) were selected. The ROIs were chosen according to the criteria proposed in previous studies,^{26,29,30} in which different shapes and sizes were applied. Images were analyzed in the axial, sagittal and coronal sections with slices of 0.25 mm for the first ROI (ROI-v), which assessed the second cervical vertebra (C2),

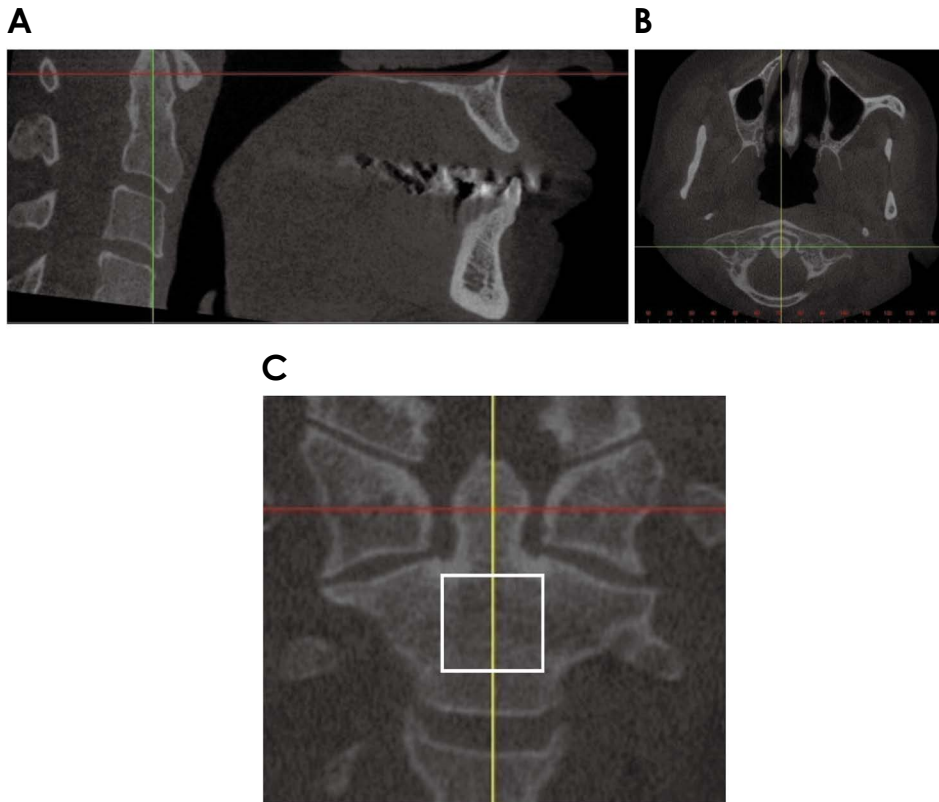


Fig. 1. Slices used for the assessment of the second cervical vertebra (C2), as well as their positions and alignments. This region of interest is standardized by calibrating the position of C2. A line is drawn passing through the dens in the sagittal plane (A) and tilting it perpendicular to the computer screen. The most central point of the dens is located in both axial (B) and coronal images (C), so that a cross marks its center.

and slices of 1.25 mm for the second ROI (ROI-m), which was selected in the mandible. After a 1-week interval, the same image analyses were repeated to evaluate the intra- and inter-observer agreement.

The ROI-v was acquired from the coronal view of C2. This ROI was selected by centering C2, using the sagittal (Fig. 1A), axial (Fig. 1B), and coronal (Fig. 1C) planes, so that a cross marked its center. The ROI-m selection started by creating a panoramic reconstruction image of the mandible. This ROI was then defined using the sagittal (Fig. 2A) and the axial (Fig. 2B) planes. The panoramic reconstruction image showed mostly trabecular bone, avoiding any cortical bone overlap (Fig. 2C). This ROI was selected on the right side of the mandible and was chosen to avoid anatomical interference from structures such as teeth, foramina, and the inferior alveolar canal. Another advantage of this position is that some patients with edentulous posterior regions are likely to have a lower bone volume due to physiological resorption. Both the vertebral (Fig. 1C) and mandibular ROIs (Fig. 2C) measured 40×40 pixels.

The images were processed and analyzed with ImageJ, a public domain software (available at <https://rsb.info.nih.gov/nih-image>). FD was analyzed through a plugin for ImageJ called BoneJ, which uses the box-counting method. Images were processed and FD was calculated based on

the protocol that has been traditionally used in studies that assessed conventional radiographs¹⁴⁻¹⁶ and was described by White and Rudolph in 1999.³² This image processing method was adapted to CBCT considering its 3-dimensional nature according to previous studies.^{16,17,32} Figure 3 illustrates the application of this protocol to the selected ROIs, with the following steps: duplication of the ROI (Fig. 3A); application of a 10-pixel Gaussian filter so that fine and medium structures were eliminated and only large variations in density remained (Fig. 3B); subtraction of the second image from the first (Fig. 3C); transformation of the resulting image into a binary 8-bit image (Fig. 3D); and skeletonization and outlining the bone trabeculae (Fig. 3E), resulting in the bone trabeculae being clearly outlined. This figure also presents a graph of the FD analysis (Fig. 3F). In total, 2 FD measures were obtained (1 for each ROI).

The images were analyzed on a high-resolution LCD computer monitor (1280×1024) in a dark environment. For intra-observer reliability, 1 observer analyzed the FD twice within a 1-week interval. For inter-observer reliability, the results of the analyses of 2 independent observers were compared. The 2 observers were oral and maxillofacial radiologists with over 4 years of experience with CBCT exams. Neither observer was aware of the DXA results.

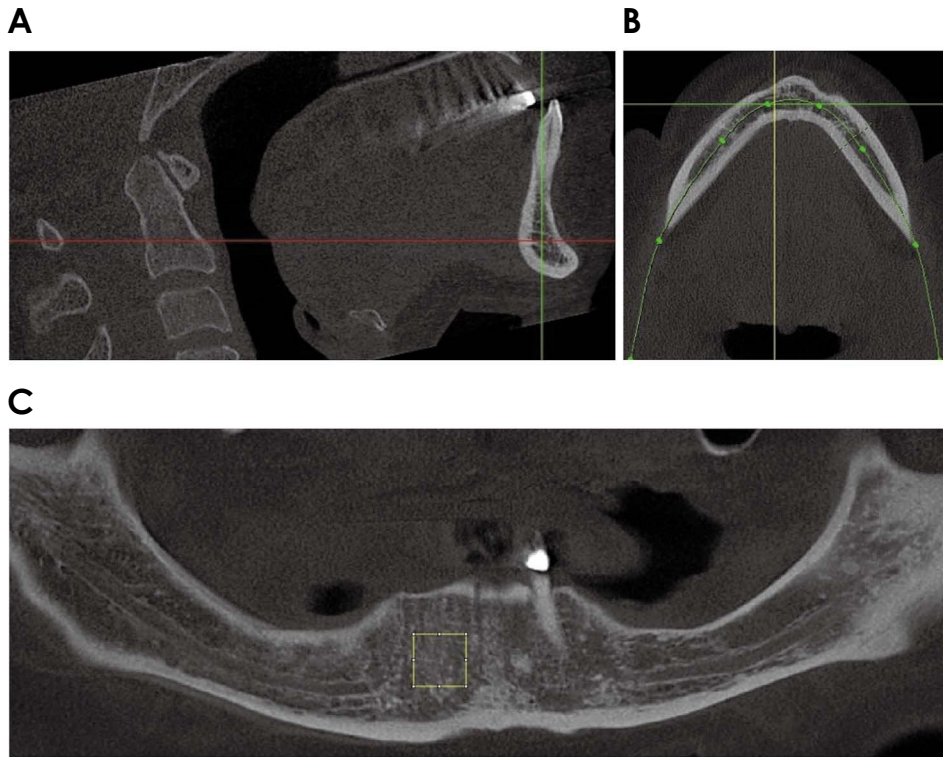


Fig. 2. Images used for assessing the mandible, including their positions and alignments. A. In the sagittal view, the mental foramen is tilted until it is also perpendicular to the computer screen. The cutting curve is drawn on the center of the axial image of the mandible (B) in order to reconstruct the panoramic image (C). The standardization aims to show mostly trabecular bone, avoiding any cortical bone overlap. C. The selected region of interest (square) at the mandibular site measures 40×40 pixels.

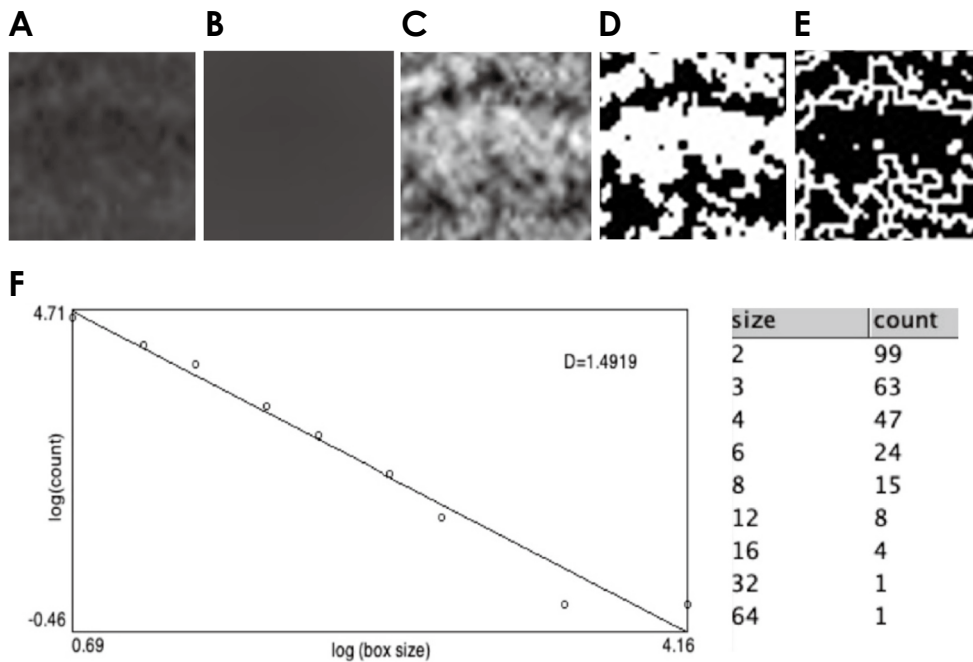


Fig. 3. Image processing method for fractal dimension analysis. A. Duplication. B. Gaussian filter at 10.00 pixels. C. Subtraction of the second image from the first. D. Conversion of the image into a binary 8-bit image. E. Skeletonization and outlining the bone trabeculae. F. The box-counting procedure and calculation are also represented by a graph.

Statistical analyses

After checking the normality of the distribution of the FD analysis results for age, height, and weight data, as well

as homoscedasticity (the Shapiro-Wilk test and Cochran test), the analyses were performed. To test the hypothesis of equality of the mean FD on each ROI, the age, height, and

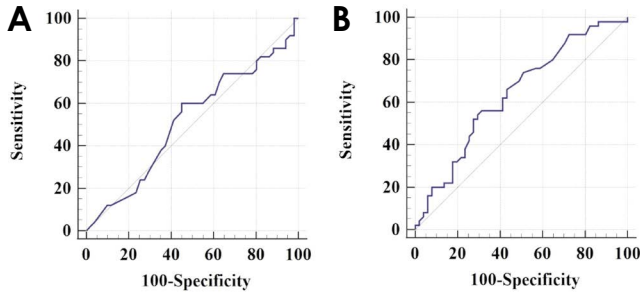


Fig. 4. Receiver operating characteristic (ROC) curves of the fractal dimension analysis at the vertebral (A) and mandibular (B) sites.

weight between the groups (women with normal BMD and osteoporosis), the Student t-test was applied to the variables that were consistent with the assumptions of normality and homoscedasticity, and the non-parametric Mann-Whitney test for the variables that were not in accordance with those assumptions. The correlations between the measurements were verified by correlation coefficients.

Receiver operating characteristic (ROC) curve analysis was used to analyze the accuracy of FD measurements in each ROI. The area under the ROC curve (AUC) was used to quantify the accuracy of the methods, as previously proposed.³³ The accuracy of FD measurements in the diagnosis of osteoporosis was calculated for the optimal thresholds.

Regarding intra- and inter-observer agreement, the calculated values of FD were compared, following the Bland and Altman method,³⁴ which results in a coefficient of repeatability for repeated measurements that is twice the standard deviation of the differences between them. According to this method, the precision of the measurements was classified as excellent (<10%), good to moderate (10 to 20%), low (>20%).

A *P* value less than 0.05 was considered to indicate statistical significance for all tests. The statistical analyses were performed in Statistica 7.0 software (ver. 7, Stat Soft, Inc, 2004, Statistica, Tulsa, OK, USA) and Medcalc 16.8.4 (Medcalc Software bvba, Ostend, Belgium).

Results

Table 1 presents a comparison of descriptive data between postmenopausal women with normal BMD and osteoporosis. The mean values for height, weight, BMD at the 3 bone sites, and FD at the mandibular site (ROI-m) were significantly lower in the osteoporotic group than in postmenopausal women with normal BMD. The mean values of FD did not present statistically significant differ-

Table 1. Comparison of mean values of descriptive data between postmenopausal women with normal bone mineral density and osteoporosis

Variables	Normal BMD	Osteoporosis
BMD L1-L4 (g/cm ²)	1.202 ± 0.131	0.797 ± 0.064**
BMD FN (g/cm ²)	1.022 ± 0.116	0.765 ± 0.101*
BMD TH (g/cm ²)	1.075 ± 0.109	0.789 ± 0.125*
FD ROI-v	1.80 ± 0.17	1.80 ± 0.18
FD ROI-m	1.76 ± 0.23	1.65 ± 0.26**
Age (years)	64.85 ± 9.78	63.94 ± 9.95
Height (cm)	157.73 ± 7.32	151.73 ± 6.34**
Weight (kg)	73.21 ± 10.85	59.07 ± 10.71*

BMD: bone mineral density, FN: femoral neck, TH: total hip, L1: first lumbar vertebra, L4: fourth cervical vertebra, FD: fractal dimension, ROI-v: region of interest in the second vertebra, ROI-m: region of interest in the panoramic reconstruction image of the mandible. *: *P* < 0.05 by the t-test, **: *P* < 0.05 by the Mann-Whitney test

Table 2. Correlation coefficients between fractal dimension measurements and bone mineral density at the lumbar spine, femoral neck, and total hip

	BMD L1-L4	BMD FN	BMD TH
ROI-v	-0.075*	-0.145*	-0.103*
ROI-m	0.059*	0.058*	0.059*

ROI-v: fractal dimension at the region of interest in the vertebral site, ROI-m: fractal dimension at the region of interest in the mandibular site, L1: first lumbar vertebra, L4: fourth lumbar vertebra, FN: femoral neck, TH: total hip, BMD: bone mineral density. **P* > 0.05 (not statistically significant)

ences at the vertebral site between both studied groups.

Regarding intra-observer agreement, most of the measurements were between the limits of agreement ($\pm 2SD$). The mean difference between the measurements was -0.02 (95% limits of agreement: -0.19 to 0.16) for ROI-v and -0.07 (95% limits of agreement: -0.63 to 0.49) for ROI-m. The precision for ROI-v was 9% and the precision for ROI-m was 35%.

In the analysis of inter-observer agreement, most of the measurements were also within the limits of agreement ($\pm 2SD$) with mean differences between the measurements of 0.2 (95% limits of agreement: -0.45 to 0.86) for ROI-v and -0.31 (95% limits of agreement: -1.05 to 0.41) for ROI-m. Lower precision was found for both ROIs than for the intra-observer values (44% for ROI-v and 55% for ROI-m).

There was no correlation between the FD analyses (ROI-v and ROI-m) and patients' age, weight and height (*P* > 0.05). FD analyses at the vertebral and mandibular sites, following the proposed method, resulted in no cor-

relation with BMD at the lumbar spine, FN and TH, as shown in Table 2.

The AUC was 0.531 ($P=0.720$) for ROI-v and 0.644 ($P=0.008$) for ROI-m. The ROC curves for the ROI-v and ROI-m are presented in Figures 4A and B, respectively. For an FD of 1.703 at the mandibular ROI (the cutoff threshold), the following accuracy measurements were obtained: sensitivity: 54.9%, specificity: 71.1%, positive predictive value: 65.1%, and negative predictive value: 61.7%.

Discussion

This study compared the FD of the vertebral and the mandibular trabecular bone between postmenopausal women with osteoporosis and normal BMD according to DXA at the lumbar spine and proximal femur. The FD analysis of the mandibular bone presented lower mean values in osteoporotic women than in women with normal BMD. However, the vertebral measurements did not differ significantly between women with normal BMD and osteoporosis.

To the authors' knowledge, this is a pioneering diagnostic test study that evaluated the accuracy of FD measurements on CBCT to identify postmenopausal women with osteoporosis. Of the 2 different measurements (ROI-v and ROI-m), only the FD of the mandible (ROI-m) demonstrated accuracy in identifying postmenopausal women with osteoporosis. Nevertheless, the accuracy of this measurement was low, with an AUC of 0.644. At an FD value of 1.7 in ROI-m, the sensitivity of FD to identify postmenopausal women with osteoporosis was 54.9% with a specificity of 71.1%. In a previous study of dental panoramic radiographs, the authors reported an AUC of 0.78 for mandibular FD to identify women with osteopenia ($T\text{-score} \leq -1.0$). With a similar cut-point of 1.7 for FD, the sensitivity was 84.6% with a specificity of 40%.¹⁶ However, it is not possible to compare these results directly. Although FD was analyzed in the mandibular trabecular bone in both studies, the use of different imaging modalities precludes a direct comparison. Moreover, in the present study, the outcome was related to osteoporotic women, whereas in the previous study the measurements were related to osteopenia.

Some studies have found differences in FD values between individuals with osteoporosis and with normal BMD.^{17,18} In contrast, FD was similar in both groups in other studies.^{14,15,35} These divergent results may be due to different methodological approaches, including image

processing for FD calculation. In the present study, a Gaussian filter at 10 pixels was used. In most previous studies with intraoral and panoramic radiographs, a Gaussian filter at 35 pixels was applied to remove brightness variations due to overlapping soft tissue and variable bone thickness.^{14-19,35} These discordant studies were based on radiographs. Therefore, these studies had substantial limitations due to the 2-dimensional representation of the images and extensive structure overlap. In contrast, in the present study, low-pass filtering was performed, based on a previous CBCT study.³²

To our knowledge, only 2 studies have compared FD analyses of the jawbones on CBCT scans with BMD determined by DXA.^{26,27} The former study compared FD between 25 women with normal BMD and 25 women with osteoporosis according to DXA only at the lumbar spine.²⁶ A circular region of interest of 20×20 pixels was selected on coronal images below the roots of the premolar and the mental foramen. A negative correlation was found between FD and lumbar spine BMD. Although the control group showed lower FD values than the osteoporotic group, no significant difference was found between the 2 groups. In our study, FD values at the mandibular trabecular bone were significantly lower in the osteoporotic group and no correlation was found between mandibular FD values and BMD at the lumbar spine, FN, or TH.

In the other aforementioned observational study that compared FD at the jawbones with BMD, FD measurements were performed in different locations: the condyle, the maxilla, and the inferior cortex of the mandible.²⁷ The ROI sizes were 40×30 , 14×14 , and 12×12 pixels, respectively. FD measurements were compared among 26 patients who had osteoporosis according to DXA at the lumbar spine and hip, 33 who had osteopenia, and 31 with a normal BMD. Only the ROI located on the left side of the maxilla showed significantly lower results in osteoporotic individuals than in the control group. The image processing method for FD analysis did not follow any traditional parameters, like the ones used by White and Rudolph in 1999.³¹

In agreement with other authors, it is possible that the discrepancies of results in all previous researches using FD measurements on dental imaging modalities could be explained by anatomical variations, the use of different methods to obtain 2-dimensional or 3-dimensional bone images, and differences in selecting the areas to be measured or in the methods applied to obtain FD results.³⁶

A recent study evaluated the reliability of FD measurements on CBCT scans. However, the authors compared

results obtained in patients with medication-related osteonecrosis of the jaw using different ROIs. The FD assessments showed good reproducibility.³⁷ The selection of ROI-v, in this study, at the cervical vertebra was based on a recent study with 38 postmenopausal women, wherein the authors found that radiographic density analysis of C2 showed a significant correlation with lumbar and femoral BMD.²⁹ The authors concluded that this ROI has great potential to detect bone changes caused by osteoporosis. However, the authors recognized that the measurement was very subjective and susceptible to variations in different exposure parameters, leading to the possibility that 2 examinations of the same patient using the same tomography device could present different results.²⁹ Some authors have demonstrated that bone structure patterns, including FD, are not affected by the exposure time. However, these bone parameters are strongly affected by the voxel size.³⁸

A recent systematic review and meta-analysis showed that, to date, FD measures on dental radiographs have not been able to distinguish individuals with osteoporosis from healthy controls with significant performance.³⁹ Studies on FD using CBCT are scarce, and there is a need for further standardized studies, especially concerning FD calculation (regions for FD assessment, image-processing techniques, and methods for FD measurement). This result is in line with the present study, which found that FD analysis at the vertebral site could not be used as a complementary tool to refer postmenopausal women for further densitometric investigation. The box-counting method was chosen to evaluate FD at 2 distinct bone sites, using 2 different image-processing methods. However, as in all previous studies that tested the correlation between FD and skeletal BMD,^{26,27} the selected ROI was bi-dimensional. Therefore, despite using a 3-dimensional imaging modality, the bone texture parameter (FD) was measured 2-dimensionally on multiplanar reconstruction images similar to conventional radiographs, with the exception of soft tissue overlap. Future studies should use software in which microstructural bone parameters could be measured 3-dimensionally. The image processing protocol should also be standardized for CBCT studies using FD.

The present study has other limitations, including the use of a convenience sample based on a DXA database. The correlation between FD and BMD was tested, which can be considered a promising bone texture image parameter related to bone quality and a parameter related to bone strength, respectively. Therefore, the association of FD or other bone texture parameters on CBCT should

also be considered in further research, as well as the inclusion of osteopenia patients.

In conclusion, based on our image processing protocol for FD analysis, lower values of FD on the mandibular trabecular bone were found in osteoporotic women than in women with normal BMD. Nevertheless, no significant differences were found in the vertebral measurements. Furthermore, none of the measurements produced highly accurate and reliable results for detecting postmenopausal women with low BMD.

Conflicts of Interest: None

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