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Structural complexity of the craniofacial trabecular bone in multiple myeloma assessed by fractal analysis

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ABSTRACT

Purpose: This study aimed to evaluate the structural complexity of craniofacial trabecular bone in multiple myeloma by fractal analysis of panoramic and lateral skull radiography, and to compare the fractal dimension values of healthy patients (HPs), pre-treatment patients (PTPs), and patients during bisphosphonate treatment (DTPs).

Materials and Methods: Pairs of digital panoramic and lateral skull radiographs of 84 PTPs and 72 DTPs were selected. After application of exclusion criteria, 43 panoramic and 84 lateral skull radiographs of PTPs, 56 panoramic and 72 lateral skull radiographs of DTPs, and 99 panoramic radiographs of age- and sex-matched HPs were selected. The fractal dimension values from panoramic radiographs were compared among HPs, PTPs, and DTPs and between anatomical locations within patient groups using analysis of variance with the Tukey test. Fractal dimension values from lateral skull radiographs were compared between PTPs and DTPs using the Student t-test. Pearson correlation coefficients were used to assess the relationship between the mandible from panoramic radiographs and the skull from lateral skull radiographs. Intra-examiner agreement was assessed using intraclass correlation coefficients ($\alpha = 0.05$).

Results: The fractal dimension values were not significantly different among HPs, PTPs, and DTPs on panoramic radiographs or between PTPs and DTPs on lateral skull radiographs ($P > 0.05$). The mandibular body presented the highest fractal dimension values ($P \leq 0.05$). The fractal dimension values of the mandible and skull in PTPs and DTPs were not correlated.

Conclusion: Fractal analysis was not sensitive for distinguishing craniofacial trabecular bone complexity in multiple myeloma patients using panoramic and lateral skull radiography. ***(Imaging Sci Dent 2022; 52: 33-41)***

KEY WORDS: Fractals; Cancellous Bone; Multiple Myeloma; Diagnostic Imaging

Introduction

Multiple myeloma (MM) is one of the most frequent haematological malignancies worldwide and directly affects bone structure. This condition is characterised by the neoplastic proliferation of monoclonal plasma cells in the bone marrow, leading to systemic effects such as anaemia, infections, hypercalcaemia, and renal failure.[1] Furthermore, osteolytic lesions throughout the skeleton can be observed, increasing the risk for pathological bone fractures, which are the most frequent complication in the course of MM.[2] These lesions are treated using intravenous bisphosphonates, which inhibit osteoclast differentiation and maturation, induce osteoclast apoptosis, and reduce the resorption of bone tissue,[3] leading to improved cancer prognosis and quality of life outcomes.

A complete examination for MM should include radiographic examinations because the craniofacial bone lesions may

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be visualised on panoramic and lateral skull radiographs as a primary manifestation.[4] The typical radiographic features of MM bone lesions in lateral skull radiographs are single or multiple well-defined and non-corticated radiolucent areas that are also referred to as "punched-out lesions." Regarding the jawbones observed in panoramic radiographs, MM may cause a myriad of changes including solitary bone lesions, multiple osteolytic lesions, diffuse osteoporosis, diffuse sclerosis, and lamina dura abnormalities.[2]

Fractal analysis is a mathematical method to quantify structural complexity that cannot be measured or calculated utilising conventional mathematical equations.[5] The resulting numerical expression is the fractal dimension (FD), which for 2-dimensional images varies between 1 and 2, indicating the lowest and highest structural complexity, respectively.[6,7] In health sciences, fractal analysis has been applied to assess the architecture of the trabecular structure when bone metabolism is affected by diseases or drugs. Some of these conditions include osteoporosis,[8,9] sickle cell anaemia,[10] hyperparathyroidism,[11] and osteogenesis imperfecta.[12]

Multiple scientific studies have subjectively assessed the radiographic characteristics of MM bone lesions;[2,13] however, considering the wide availability of high-quality digital images and modern objective techniques, accurate quantitative methods could be useful in identifying events undetectable by the human eye. Interestingly, a previous study found that the FD was significantly associated with the presence of vertebral fractures in MM patients; however, only thoracic and lumbar spine images were used.[14] Thus, the aim of this study was 1) to objectively evaluate the structural complexity of the craniofacial trabecular bone in MM by fractal analysis of panoramic and lateral skull radiography, and 2) to compare the FD values of patients before and during treatment with intravenous bisphosphonates.

Materials and Methods

Ethical aspects

The research protocol was approved by the local research ethics committee (#2.526.565). The authors read the Helsinki Declaration and followed the guidelines in this investigation. All subjects voluntarily signed an informed consent form.

Sample selection

Pairs of digital panoramic and lateral skull radiographs of 84 patients diagnosed with MM before treatment (pre-treatment patients; PTPs) and 72 other patients during treatment for MM with intravenous bisphosphonates for at least 6 months (during-treatment patients; DTPs) were selected from the records of a dental oncology service. The exclusion criteria were radiographic images of unacceptable technical quality including severe positioning errors and of patients with local or systemic diseases that affected bone density, temporomandibular joint disorders, and maxillofacial pathologies such as cystic lesions and solid intraosseous tumours.

Application of the exclusion criteria resulted in a total of 43 panoramic radiographs (23 men, 20 women; mean age: 62.94 years; range: 30-90 years) and 84 lateral skull radiographs (40 men, 44 women; mean age: 62.94 years; range: 30-90 years) from PTPs, and 56 panoramic radiographs (35 men, 21 women; mean age: 63.54 years; range: 33-92 years) and 72 lateral skull radiographs (45 men, 27 women; mean age: 63.54 years; range: 33-92 years) from DTPs. Digital panoramic radiographs of age- and sex-matched healthy patients (HPs) were also selected (n = 99) and served as controls for MM patients. All radiographs were coded to protect the privacy of patients' health information.

Image acquisition specifications

All selected panoramic and lateral skull radiographs were obtained using the same PaX-400 digital extra-oral imaging system (Vatech Global, Hwaseong, Korea) for reasons unrelated to the present study. The patients were positioned with the Frankfurt plane parallel to the floor and the mid-sagittal plane parallel to the vertical plane for both techniques, taking into account individual limitations of cervical movement in older patients with MM.

The radiographic exposure parameters were automatically adjusted with the selection of the patient size in the extra-oral imaging system and, if needed, the resulting radiographic image had the brightness, contrast, and/or gamma level slightly fine-tuned for image standardisation. All images were exported as TIFF files.

Selection of regions of interest

In a quiet environment with reduced lighting, regions of interest were selected on all images using the ImageJ 1.44o software, a public domain software developed by the National Institutes of Health (Bethesda, MD, USA), and a 24.1-inch LCD monitor (MDCR-2124, Barco, Kortrijk, Belgium) with a resolution of 1920 × 1200 pixels.

In the panoramic radiographs, 4 regions of interest were selected on the trabecular bone of both sides of the mandible (Fig. 1), as follows: 1) the centre of the mandibular condyle with a dimension of 75 × 75 pixels; 2) the mandibular ramus between the anterior cortices of the ramus and the

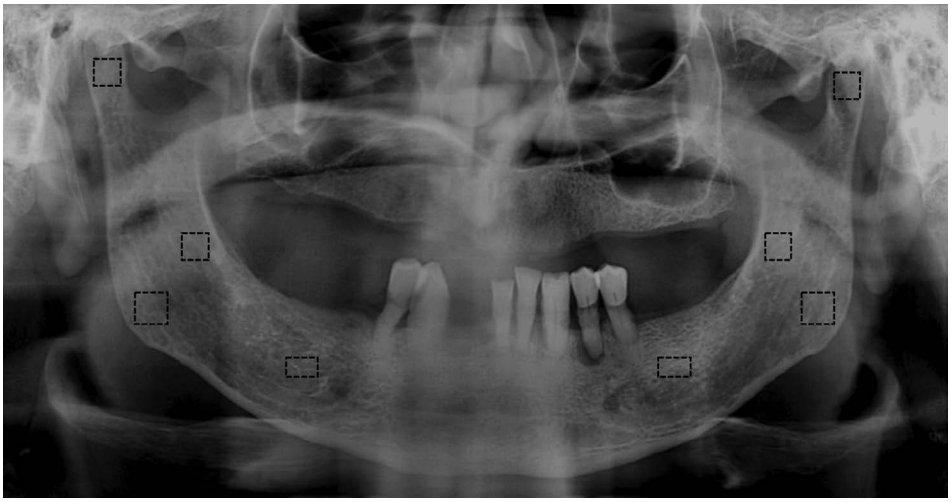

Fig. 1. Location of the regions of interest on the trabecular bone of both sides of the mandible on a panoramic radiograph.

mandibular canal, at the level of the occlusal plane with a dimension of 75 × 75 pixels; 3) the mandibular body between the alveolar bone crest and the base of the mandible, posterior to the mental foramen with a dimension of 98 × 62 pixels (width × height); and 4) the mandibular angle above the gonion (a cephalometric landmark) with a dimension of 100 × 100 pixels. The regions of interest were selected to avoid the mandibular cortical bone, tooth root, and severe panoramic-related ghost images. Figure 2 shows representative panoramic radiographs with a region of interest in the right mandibular body (black rectangle) of an HP, PTP, and DTP.

In the lateral skull radiographs, a rectangular region of interest was selected in the centre of the neurocranium, such that the largest possible area was covered without including the cortices of the calvaria, sphenoid bone, and petrous part of the temporal bone (Fig. 3).

Fractal analysis

Following a previously described methodology,[15] all regions of interest were individually subjected to the following sequence of digital processing steps prior to the fractal analysis: blurring, subtraction, addition, binarisation, erosion, dilation, inversion, and skeletonisation (Fig. 4).

The original image of each region of interest (Fig. 4A) was blurred to remove brightness discrepancies (Fig. 4B), and the resulting blurred image was subtracted from the original image to attenuate large variations in pixel intensity (Fig. 4C). A pixel intensity value of 128 was then added to all pixels of the subtracted image to shift the histogram to the centre of an 8-bit grayscale (Fig. 4D). At this point, only important contrast between the trabecular bone and marrow space was preserved. The resulting image was then binarised to store each pixel as a single bit (trabecular bone as white and marrow space as black) (Fig. 4E), eroded (Fig. 4F) and dilated (Fig. 4G) to provide more accurate pixel values along the edges of the image. Finally, the resulting image was inverted to outline the trabecular bone in black (Fig. 4H) and skeletonised to exhibit only the most central pixel lines (Fig. 4I).

The FD was then calculated for each skeletonised image using the box-counting method,[5] also referred to as the Minkowski-Bouligand dimension, which is based on the relationship between different box sizes and the consequent number of boxes required to cover complex zones of the image. Three representative fractal box-counting graphs are shown in Figure 5. Fifteen days after the completion of the fractal analysis of all images, 30% of the total sample was re-evaluated to test the reproducibility of the method.

Statistical analysis

The collected data were recorded and tabulated in SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Intra-examiner agreement was evaluated using the intraclass correlation coefficient (ICC) and interpreted according to the Cicchetti and Sparrow categorisation system,[16] in which ICCs of <0.40, 0.40-0.59, 0.60-0.74, and 0.75-1.00 indicate poor, fair, good, and excellent agreement, respectively.

The FD obtained from the panoramic radiographs were compared between HPs, PTPs, and DTPs using 1-way analysis of variance (ANOVA). The FD values from the same patient group were also compared for each anatomical region (condyle, ramus, body, and angle) using 1-way ANOVA. Different anatomical regions of the mandible were compared within the same patient group using 1-way ANOVA with the Tukey post-hoc test. The level of significance was set at

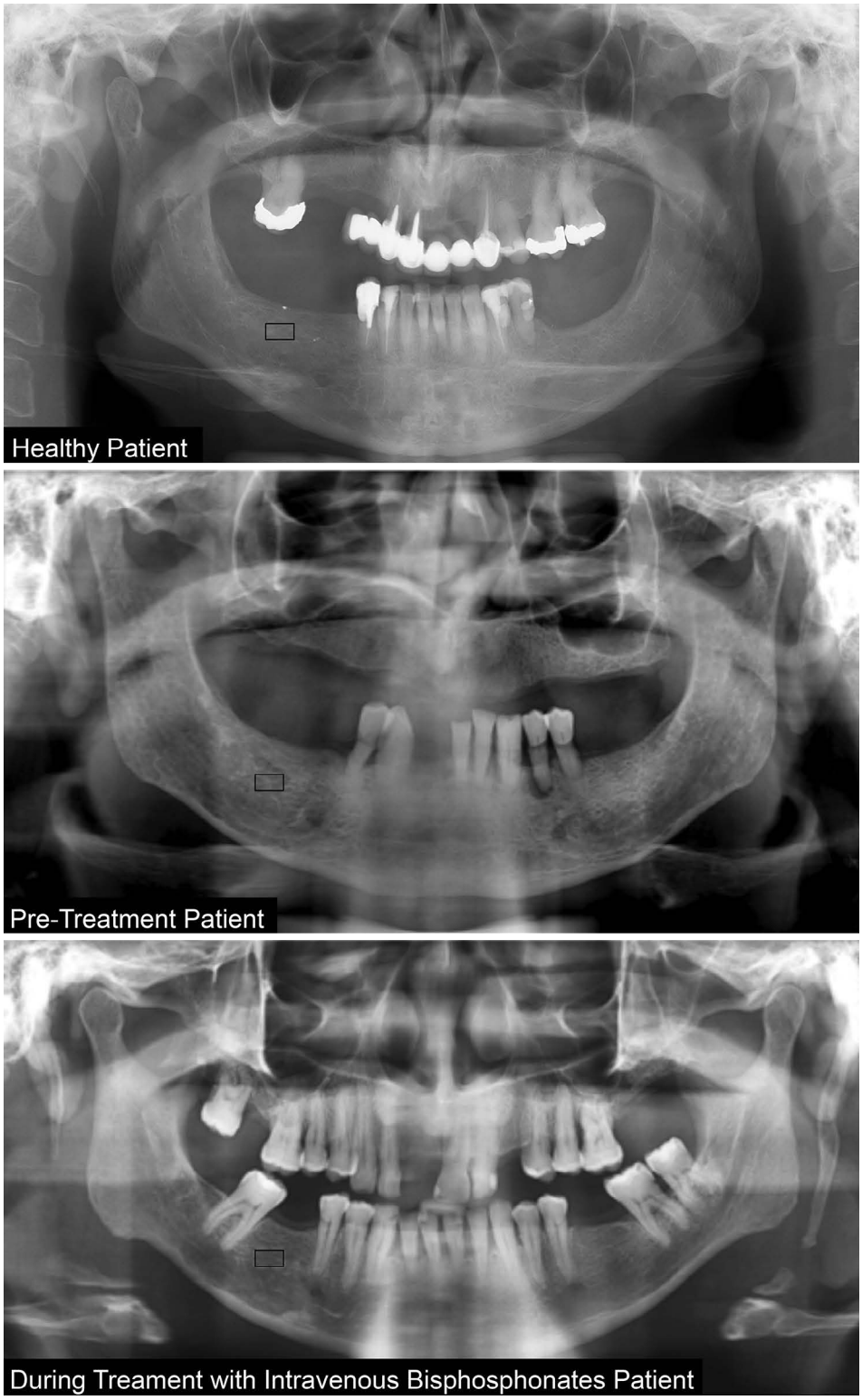

Fig. 2. Representative panoramic radiographs with a region of interest in the right mandibular body (black rectangle) of a healthy patient, pre-treatment patient, and during intravenous bisphosphonate treatment patient, respectively. The 3 panoramic radiographs are from different patients.

5% ($\alpha = 0.05$).

The FD values obtained from the lateral skull radiographs were compared between PTP and DTP using the Student t-test.

The Pearson correlation test was used to measure the statistical relationship between the FD values from the mandible and those from the skull in both PTPs and DTPs. This analysis included only pairs of panoramic and lateral skull radiographs from the same patients (43 pairs for PTPs and 56 pairs for DTPs).

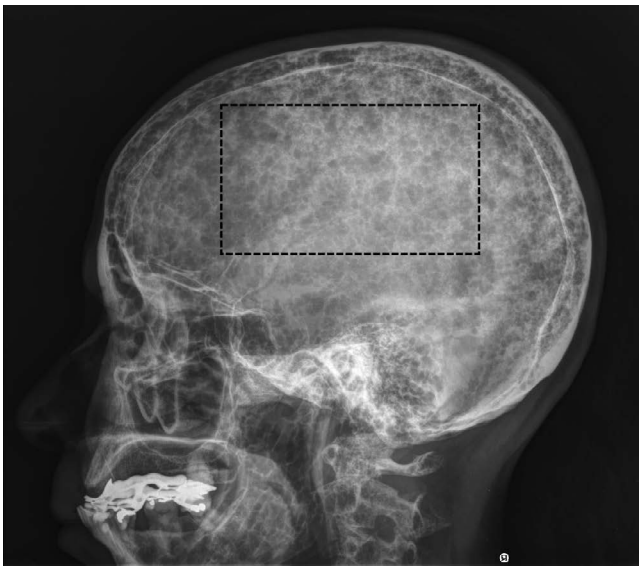

Fig. 3. Location of the region of interest (black rectangle) on the trabecular bone of the neurocranium on a lateral skull radiograph.

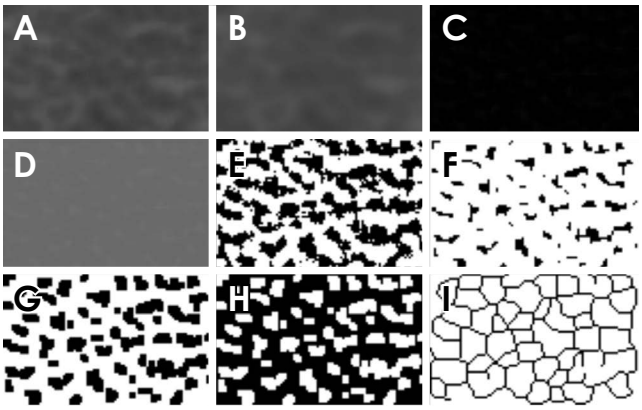

Fig. 4. Digital image processing for the fractal analysis of a representative region of interest (A. Original image, B. Blurred, C. Subtracted, D. Added, E. Binarised, F. Eroded, G. Dilated, H. Inverted, I. Skeletonised).

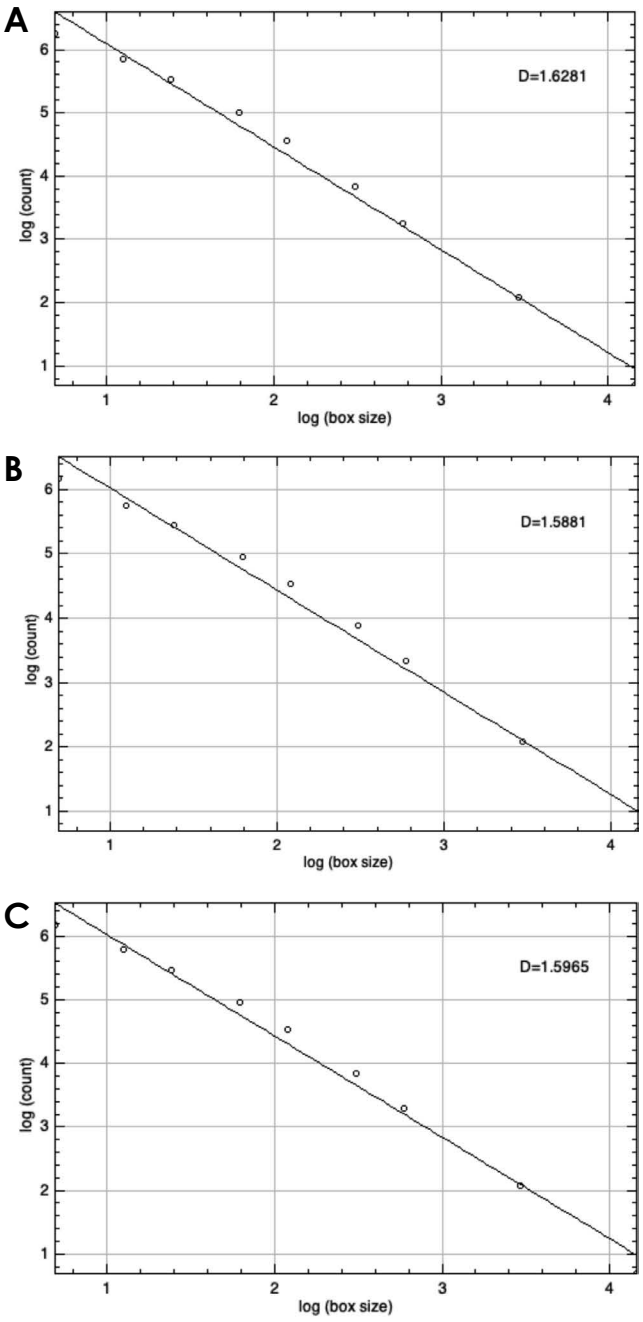

Fig. 5. Box-counting dispersion graphs from the region of interest in the right mandibular body on the panoramic radiographs shown in Figure 2: A. healthy patient, B. pre-treatment patient, and C. during intravenous bisphosphonate treatment patient. Note the inversely proportional relationship between box count and box size. D is the numerical expression of the resulting trend line and indicates the fractal dimension value.

Results

The ICC revealed excellent reproducibility of the fractal analysis for both panoramic radiographs (ICC = 0.97, $P < 0.05$) and lateral skull radiographs (ICC = 0.99, $P < 0.05$).

As shown in Table 1, the FD values from panoramic radiographs were not significantly different between HPs, PTPs, and DTPs ($P > 0.05$). Similarly, as shown in Table 2, the FD values from the same anatomical region on panoramic radiographs were not significantly different between HPs, PTPs, and DTPs ($P > 0.05$). Within the same patient group, the FD values were significantly greater in the mandibular body and significantly lower in both the condyle and mandibular ramus ($P \leq 0.05$) (Table 2).

For the lateral skull radiographs, no statistically significant differences were observed in the mean values of FD between PTPs and DTPs ($P > 0.05$) (Table 3). Furthermore, as shown in Figures 6 and 7, no correlation was found between the

Table 1. Fractal dimension values from panoramic radiographs of different patient groups: pre-treatment patients (PTPs), during bisphosphonate treatment patients (DTPs), and healthy patients (HPs)

Patient group	Mean	Standard deviation	95% confidence interval per mean		Minimum	Maximum
			Lower bound	Upper bound		
PTPs	1.50	0.01	1.50	1.51	1.48	1.55
DTPs	1.50	0.01	1.50	1.51	1.47	1.53
HPs	1.50	0.03	1.49	1.51	1.24	1.55
Total	1.50	0.02	1.50	1.5	1.24	1.55

($P>0.05$)

Table 2. Mean values (standard deviation) of the fractal dimension from panoramic radiographs as a function of the mandibular anatomical region and the patient groups

Patient group	Mandibular anatomical region			
	Body	Angle	Ramus	Condyle
PTPs	1.60 (0.02)*	1.55 (0.03)	1.42 (0.02)$^{\#}$	1.43 (0.02)$^{\#}$
DTPs	1.61 (0.03)*	1.55 (0.03)	1.43 (0.03)$^{\#}$	1.43 (0.03)$^{\#}$
HPs	1.61 (0.05)*	1.55 (0.06)	1.43 (0.05)$^{\#}$	1.42 (0.05)$^{\#}$

PTPs: pre-treatment patients, DTPs: during bisphosphonate treatment patients, HPs: healthy patients. *: significantly greater than the other mandibular regions, $^{\#}$: significantly lower than the other mandibular regions.

Table 3. Fractal dimension values from lateral skull radiographs of the pre-treatment patients (PTPs) and during treatment (with bisphosphonates) patients (DTPs)

Patient group	N	Mean	Standard deviation	Standard error of the mean
PTPs	84	1.46	0.14	0.01
DTPs	72	1.48	0.11	0.01

($P>0.05$)

panoramic and lateral skull radiographs in either PTPs or DTPs.

Discussion

In dentistry and medicine, fractal analysis is used to study the complexity of trabecular bone and the effects of diverse pathological conditions.[5,17,18] When significant differences are observed between HPs and affected patients, fractal analysis can be further discussed as a potential predictive method for the disease in question. In the present study, fractal analysis was performed for a relatively large sample of patients with MM using panoramic and lateral skull radiography, but no significant differences from HPs were detec-

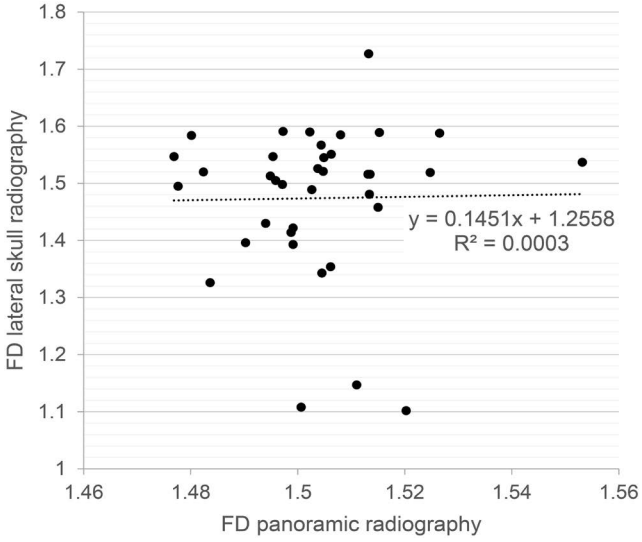

Fig. 6. Dispersion graph correlating fractal dimension (FD) values from panoramic radiographs with those from lateral skull radiographs in pre-treatment patients.

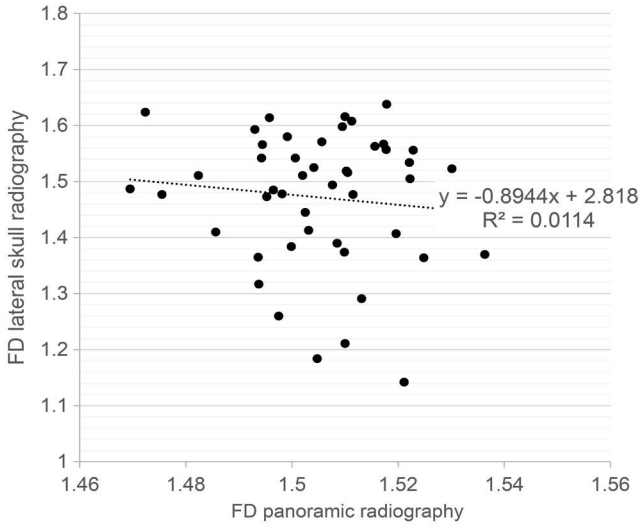

Fig. 7. Dispersion graph correlating fractal dimension (FD) values from panoramic radiographs with those from lateral skull radiographs during intravenous bisphosphonate treatment patients.

ted. Furthermore, the possible effect of treatment with intravenous bisphosphonates for MM on the complexity of the craniofacial trabecular bone was not found to be significant in this study.

This absence of significant differences was not expected in this study mainly because of the major visual alterations observed in some patients with MM. However, this contributes to the hypothesis that, although the thin trabeculae may be apparently gone in some PTPs and DTPs, thicker zones should be preserved to a sufficient degree that they are not excluded after the skeletonisation process, and, as a consequence, do not affect the FD values. This is similar to the results reported by Mostafa et al.[19] in 2016, who studied the potential effect of osteoporosis on the trabecular bone, and Kurşun-Çakmak and Bayrak[20] in 2018, who assessed type 1 and type 2 diabetes mellitus. In both studies, significant differences were not found between patient groups. In the present study, the sample was balanced with regard to the different radiographic aspects of MM. Nonetheless, the standard deviation of FD values in both PTPs and DTPs was very low (Table 2), reinforcing the low sensitivity of fractal analysis even in patients with such heterogeneous conditions.

Nonetheless, other studies reported reduced FD values in the alveolar bone of the mandible of patients using aromatase inhibitors[21] and with chronic renal failure,[22] as well as in the condylar trabecular bone of patients with degenerative changes of the temporomandibular joint.[18] Conversely, increased FD values were observed in the periapical tissues after successful cases of endodontic treatment[23] and found to be associated with a lower probability of thoracic and lumbar vertebral fracture in MM patients.[14]

Although the main subjective imaging features of MM are well described in the scientific literature, little is known regarding objective and quantitative aspects. Removing the subjective bias of imaging evaluation is important due to the possibility of detecting early pathological alterations in bone tissue not yet visualised by the human eye.[23] In addition, in MM, this objective evaluation can be easily performed on frequently requested images, such as digital panoramic and lateral skull radiographs.

An immediate therapeutic approach for symptomatic patients with MM bone lesions, anaemia, hypercalcaemia, renal lesions, amyloidosis, or recurrent bacterial infections should be considered in light of the increased survival rate.[24] Because radiographic examinations aid in the detection of bone lesions, it is important to evaluate these examinations objectively. If any significant differences had been detected in the present study between patient groups, it would have supported the possibility of suggesting early treatment according to the patients' age and general state of health. Furthermore, the intravenous use of bisphosphonates in the treatment of bone lesions inhibits osteoclast-mediated resorption, reducing pain, hypercalcaemia, and the incidence of fractures, as well as having a direct antitumour effect.[2] This is why the present methodological design included a group of DTPs who received bisphosphonates.

Demiralp et al.[25] found higher FD values in patients using bisphosphonates and suggested that this was related to a possible decrease in bone resorption. However, this is not consistent with the present study, which did not find significant differences between PTPs and DTPs. It is worth mentioning 2 major differences between these studies that may explain the divergent results: the present study had 1) a larger sample of MM patients (72 versus 33 patients), which is relatively more representative, and 2) a shorter period of bisphosphonate treatment since the inclusion criteria considered at least 6 months of administration, whereas Demiralp et al.[25] had a mean administration period of 28 months, which may have led to more detectable bone changes. Furthermore, the type and administration of the bisphosphonates were not the same for all patients in the DTP group, which could be considered a limitation of the present study.

In addition, the results of the present study showed no correlation of the mean values of FD between panoramic and lateral skull radiographs, which eliminates the possibility of obtaining similar information in terms of fractal analysis from both imaging modalities. This absence of a correlation may have occurred due to inherent trabecular bone patterns from different regions; in the skull, bone is predominantly corticated, whereas in the mandible, the selected regions of interest encompassed trabecular regions. This is in agreement with the study of Southard et al.,[26] which demonstrated that FD values of the alveolar process were not related to the density of the spine, hip, or rib. Mostafa et al.[19] found a negative correlation between FD values and bone mineral density of the lumbar spine, but, in this case, the authors compared 2 objective methods for the assessment of the same bone. In this study, when the FD values of different mandibular anatomical regions were compared for the same group of patients, the mandibular body presented the highest FD values when compared to the angle, ramus, and condyle, and the ramus and the condyle had the lowest FD values for all patient groups. This might indicate that the masticatory stimuli in the mandibular body increase the structural complexity of the trabecular bone in this region. Conversely, the mandibular condyle is also subjected to relevant masticatory forces, but revealed the lowest FD values and did not differ from the mandibular ramus, which highlights a possible

non-linear relationship between the stress caused by mechanical forces and FD values. Interestingly, as observed in Table 2, the FD presented fairly low standard deviation for the same mandibular anatomical regions, demonstrating a site-specific trend among patients.

The selection of the regions of interest was a challenge in the present study design because of the heterogeneous radiographic aspects of MM even in different regions in the same patient. Initially, the authors tried to standardise the dimensions of all ROIs; however, when assessing the whole sample, some dimensional adjustments for the same anatomical region were needed to cover representative areas while avoiding cortical bone, tooth roots, and severe panoramic-related ghost images. Despite this, the regions of interest selected in the same anatomical zone from different patients and sides (right × left) had the same exact dimensions.

Although panoramic radiography presents multiple limitations - namely magnification, distortion, relatively low spatial resolution, major superimposition, and ghost images - it is a well-accepted complementary examination that offers wide visualisation of the jaws and dental conditions at a relatively low radiation dose and may be considered a useful tool to detect osteolytic lesions of the maxillofacial complex in MM patients.[2,4,21] Lateral skull radiography was also included since it is part of the initial diagnosis of MM lesions in the skull. Importantly, for each newly diagnosed MM patient, the International Myeloma Working Group recommends a complete radiographic evaluation, including the skull; cervical, thoracic, and lumbar spine; chest; pelvis; and long proximal bones. The use of 2-dimensional images may constitute a relevant limitation of this study, mainly because of the superimposition of the bone trabeculae and the difficulty of standardising the location of the region of interest, which, in some cases, did not include areas of visible lesions. However, a previous study performing fractal analysis in cone-beam computed tomographic images did not find significant differences between 28 HPs and 33 MM patients receiving therapy with bisphosphonates.[27] Further studies evaluating the 3-dimensional aspects of these bone lesions are recommended for a better understanding of the dynamics of bone metabolism in MM.

In conclusion, fractal analysis was not sensitive for distinguishing craniofacial trabecular bone complexity in patients with MM using panoramic and lateral skull radiography.

Acknowledgments

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Conflicts of Interest: None

References

1. Packard E, Shahid Z, Groff A, Patel R, Jain R. Multiple myeloma in an agricultural worker exposed to pesticides. Cureus 2019; 11: e4762.
2. Faria KM, Brandão TB, Silva WG, Pereira J, Neves FS, Alves MC, et al. Panoramic and skull imaging may aid in the identification of multiple myeloma lesions. Med Oral Patol Oral Cir Bucal 2018; 23: e38-43.
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. Faria KM, Ribeiro AC, Brandão TB, Silva WG, Lopes MA, Pereira J, et al. Radiographic patterns of multiple myeloma in the jawbones of patients treated with intravenous bisphosphonates. J Am Dent Assoc 2018; 149: 382-91.
5. Kato CN, Barra SG, Tavares NP, Amaral TM, Brasileiro CB, Mesquita RA, et al. Use of fractal analysis in dental images: a systematic review. Dentomaxillofac Radiol 2020; 49: 20180457.
6. Grizzi F, Castello A, Qehajaj D, Russo C, Lopci E. The complexity and fractal geometry of nuclear medicine images. Mol Imaging Biol 2019; 21: 401-9.
7. Oliveira-Santos N, Michels M, Freitas DQ, Haiter-Neto F, Oliveira ML. Influence of phosphor plate-based radiographic image specifications on fractal analysis of alveolar bone. Oral Surg Oral Med Oral Pathol Oral Radiol 2019; 128: 418-23.
8. Oliveira ML, Pedrosa EF, Cruz AD, Haiter-Neto F, Paula FJ, Watanabe PC. Relationship between bone mineral density and trabecular bone pattern in postmenopausal osteoporotic Brazilian women. Clin Oral Investig 2013; 17: 1847-53.
9. Chen Q, Bao N, Yao Q, Li ZY. Fractal dimension: a complementary diagnostic indicator of osteoporosis to bone mineral density. Med Hypotheses 2018; 116: 136-8.
10. Demirbaş AK, Ergün S, Güneri P, Aktener BO, Boyacıoğlu H. Mandibular bone changes in sickle cell anemia: fractal analysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008; 106: e41-8.
11. Ergün S, Saraçoğlu A, Güneri P, Özpınar B. Application of fractal analysis in hyperparathyroidism. Dentomaxillofac Radiol 2009; 38: 281-9.
12. Apolinário AC, Sindeaux R, de Souza Figueiredo PT, Guimarães 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.
13. Angtuaco EJ, Fassas AB, Walker R, Sethi R, Barlogie B. Multiple myeloma: clinical review and diagnostic imaging. Radiology 2004; 231: 11-23.
14. Oravec D, Yaldo O, Bolton C, Flynn MJ, van Holsbeeck M, Yeni YN. Digital tomosynthesis and fractal analysis predict pre-

valent vertebral fractures in patients with multiple myeloma: a preliminary in vivo study. AJR Am J Roentgenol 2019; 213: W38-44.
15. White SC. Oral radiographic predictors of osteoporosis. Dentomaxillofac Radiol 2002; 31: 84-92.
16. Cicchetti DV, Sparrow SA. Developing criteria for establishing interrater reliability of specific items: applications to assessment of adaptive behavior. Am J Ment Defic 1981; 86: 127-37.
17. Sánchez I, Uzcátegui G. Fractals in dentistry. J Dent 2011; 39: 273-92.
18. Arsan B, Köse TE, Çene E, Özcan İ. Assessment of the trabecular structure of mandibular ondyles in patients with temporomandibular disorders using fractal analysis. Oral Surg Oral Med Oral Pathol Oral Radiol 2017; 123: 382-91.
19. Mostafa RA, Arnout EA, Abo El-Fotouh MM. Feasibility of cone beam computed tomography radiomorphometric analysis and fractal dimension in assessment of postmenopausal osteoporosis in correlation with dual X-ray absorptiometry. Dentomaxillofac Radiol 2016; 45: 20160212.
20. Kurşun-Çakmak EŞ, Bayrak S. Comparison of fractal dimension analysis and panoramic-based radiomorphometric indices in the assessment of mandibular bone changes in patients with type 1 and type 2 diabetes mellitus. Oral Surg Oral Med Oral Pathol Oral Radiol 2018; 126: 184-91.
21. Göller Bulut D, Bayrak S, Uyeturk U, Ankarali H. Mandibular indexes and fractal properties on the panoramic radiographs of the patients using aromatase inhibitors. Br J Radiol 2018; 91: 20180442.
22. 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.
23. Takasu M, Tani C, Ishikawa M, Date S, Horiguchi J, Kiguchi M, et al. Multiple myeloma: microstructural analysis of lumbar trabecular bones in patients without visible bone lesions - preliminary results. Radiology 2011; 260: 472-9.
24. Pittari G, Costi D, Raballo M, Maulucci L, Baroni MC, Mangoni M. Intravenous neridronate for skeletal damage treatment in patients with multiple myeloma. Acta Biomed 2006; 77: 81-4.
25. Demiralp KÖ, Kurşun-Çakmak EŞ, Bayrak S, Akbulut N, Atakan C, Orhan K. Trabecular structure designation using fractal analysis technique on panoramic radiographs of patients with bisphosphonate intake: a preliminary study. Oral Radiol 2019; 35: 23-8.
26. Southard TE, Southard KA, Jakobsen JR, Hillis SL, Najim CA. Fractal dimension in radiographic analysis of alveolar process bone. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996; 82: 569-76.
27. Feitosa ÉF, Vasconcellos MM, Magalhães RJ, Domingos-Vieira AC, Visconti MA, Guedes FR, et al. Bisphophonate alterations of the jaw bones in individuals with multiple myeloma. Dentomaxillofac Radiol 2020; 49: 20190155.