Evaluation of texture imaging parameters on panoramic radiographs of patients with Sheehan's syndrome: A STROBE-compliant case-control study

Davi de Sá Cavalcante[1], Mac Gayver da Silva Castro[2], Ana Rosa Pinto Quidute[3], Manoel Ricardo Alves Martins[3], Adília Mirela Pereira Lima Cid[1], Paulo Goberlânio de Barros Silva[1], James Cadwell Williams Jr[4], Frederico Sampaio Neves[5], Thyciana Rodrigues Ribeiro[1], Fábio Wildson Gurgel Costa[1]*

[1]Department of Clinical Dentistry, Postgraduate Program in Dentistry, Federal University of Ceará, Fortaleza, Brazil

[2]Realistic Simulation Center, Univeristy Center UNICHRISTUS, Fortaleza, Brazil

[3]Division of Endocrinology and Diabetology, Walter Cantídio University Hospital, Fortaleza, Brazil

[4]Department of Anatomy and Cell Biology, Indiana University-Purdue University Indianapolis, Indianapolis, IN, USA

[5]Division of Oral Radiology, School of Dentistry, Federal University of Bahia, Bahia, Brasil

*Address for correspondence and reprint requests to Fábio Wildson Gurgel Costa: Rua Alexandre Baraúna, 949, Rodolfo Teofilo, CEP: 60430-160, Fortaleza, Ceará, Brasil. Federal University of Ceará, Department of Clinical Dentistry, School of Dentistry. Telephone number: +55(85)33668232. Email: fwildson@yahoo.com.br

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ABSTRACT

Objectives: Sheehan's syndrome (SSH) is an important public health problem characterized as postpartum hypopituitarism secondary to obstetric complications-related ischemic pituitary necrosis that shows significant systemic metabolic repercussion. Thus, this study aimed to evaluate texture parameters in digital panoramic radiographs of patients with SSH.

Methods: A case-control study was conducted with 30 SSH patients from an Endocrinology and Diabetology Service of reference in Brazil, and 30 age- and sex-matched healthy controls. A custom computer program measured fractal dimension, lacunarity and some morphologic features in the following mandibular regions of interest (50x50 pixels): below the mental foramen (F1), between the first and second molars (M1), and center of the mandibular ramus (R1).

Results: The fractal analysis showed a statistically significant difference between the studied groups in all regions of interest. The fractal dimension in F1 ($p = 0.016$), M1 ($p = 0.043$), and R1 ($p = 0.028$) was significantly lower in SSH group, as well as lacunarity in R1 ($p = 0.008$). Additionally, several morphologic features were statistically significant in the SSH group ($p < 0.05$).

Conclusion: Therefore, individuals with SSH showed altered imaging texture parameters on panoramic radiographs, which reflect a smaller spatial organization of the bone trabeculae and, possibly, a state of reduced mineral bone density.

Keywords: Sheehan's syndrome, texture imaging parameters, mineral bone density, panoramic radiograph.

Introduction

The role of the pituitary-bone axis in skeletal pathophysiology has been widely recognized throughout the last decades.[1] Pituitary hormones play an important connection with skeleton-related bone metabolism because bone cells usually express hormone receptors for growth hormone, follicle stimulating hormone, thyroid stimulating hormone, adrenocorticotrophic hormone, prolactin, oxytocin and vasopressin, and their role are evident especially in several diseases.[2,3] Among the disturbances that can affect the pituitary gland, Sheehan's syndrome (SSH) is a disease that affects the secretion of adenohypophyseal hormones. This condition is known as postpartum pituitary necrosis, and it is a rare condition that was firstly reported in 1937 by HL Sheehan and co-authors that described 12 cases of gland necrosis and pituitary failure following obstetric complications.[4]

SSH is characterized by a hormonal insufficiency due to hypovolemia secondary to an excessive loss of blood during or even after delivery, which may be a result from glandular hyperplasia during pregnancy caused by the greater production of gestational hormones during this period.[5] In this situation, the gland becomes more vulnerable to a total or partial necrosis due to ischemia caused by hypovolemic shock, since poor blood supply to the anterior region of the pituitary gland impairs its function because of possible ischemia during or after childbirth.[5,6] Clinically, these findings impact in a hormonal deficiency, which possess an individual variability, ranging from impairment of a single tropic hormone to classic panhypopituitarism,[7] and they may develop a spectrum of manifestations, such as agalactia (failure of postpartum lactation), amenorrhea (failure of postpartum menstruation), adynamia (muscle weakness), adrenocortical insufficiency, clinical findings related to secondary hypothyroidism, fine wrinkling around mouth and eyes, diabetes insipidus, and empty sella.[8]

In spite of epidemiological studies regarding clinical symptoms observed in SSH,[9-11] recent researches have focused on the bone microarchitecture and its osteoporotic pattern. Agarwal et al[12] evaluated a large group of woman with SSH and found low bone mass among these individuals after assessment by dual-energy X-ray absorptiometry (DXA). Although osteoporosis has been commonly evaluated by non-invasive procedures such as DXA,[13] trabecular microarchitecture requires invasive techniques to be adequately assessed.[14] In order to obtain morphologic characteristics by

non-invasive methods, it has been used bone textural analysis in dental radiographs[15-19] and computed tomography.[20,21]

Fractal analysis is a non-invasive imaging tool to obtain data regarding bone microarchitecture, and it has been used in several studies in the field of dentomaxillofacial radiology.[22-29] In endocrine pathologies, fractal analysis and other textural imaging tools (e.g., lacunarity and morphologic aspects) have been proposed to evaluate osteoporosis,[19,30-32] osteogenesis imperfecta,[33] hyperparathyroidism,[34] chronic renal failure,[35] sickle cell anemia,[36] and diabetes mellitus.[37] To date, there are no published reports evaluating these parameters in panoramic radiographs of SSH individuals. Thus, this investigation aimed to analyze panoramic radiograph texture features of SSH in comparison with non-syndromic pared individuals.

Materials and methods

Study design

A case-control study was conducted following Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statements (https://www.strobe-statement.org/). The cases were represented by patients diagnosed with SSH under medical follow-up, and the controls were non-SSH individuals matched by sex and age.

Setting

Sample was obtained from the Endocrinology and Diabetology Service of the Walter Cantídio University Hospital (Fortaleza, Ceará, Brazil), which concentrates a significant SSH casuistry in Brazil. It was recruited volunteers who were under follow-up for more than ten years and volunteers matched by sex and age who agreed to participate in the study after reading, understood and signed a written informed consent form (research protocol # 983 022 approved by the Ethics Committee of the Federal University of Ceará).

Sample selection

The population included all patients presenting previous history of classic surgical-related haemorrhage and other obstetric and hormonal complications related to SSH diagnosis (n = 66). During the recruitment phase, it was included patients with a proven diagnosis of SSH under a routine ambulatory follow-up and those that consented to participate in this

research. The individuals were excluded if they comply with at least one of the following reasons: no attendance at routine medical appointments, no return to phone calls, death, or inability to perform panoramic radiography. After this phase, 30 volunteers were submitted to anamnesis, and they were required to perform digital panoramic radiography at the Dental Imaging Service of the Faculty of Pharmacy, Dentistry, and Nursing (Federal University of Ceará). In order to provide a case-control methodological design, for each case a non-SSH sex- and age-matched volunteer that did not show any systemic alterations that could interfere in bone metabolism were recruited. Thus, 60 individuals participated in this study as shown in Figure 1.

Quantitative variables

The quantitative variables assessed were fractal dimension, lacunarity, and morphological parameters related to the trabecular bone (trabecular area, periphery, total length of trabeculae, number of end points, and number of branching points).

Data sources/measurement

Obtaining and evaluating of digital panoramic radiographs:

Standardized digital panoramic radiographs were obtained by using Kodak K9000 3D (Kodak Dental Systems, Carestream Health, Rochester, NY, EUA) with a 14-bit grayscale (16384 greylevel), exposure time of 13.9 seconds, 65 kV, and 10 mA. Each patient was positioned using a chin rest and head stabilizer in the focal layer. A horizontal reference line was then superimposed on the patient's Frankfort horizontal plane as a technical standardization adopted during image acquisition. The Frankfort plane was positioned parallel to the ground and the median sagittal plane was perpendicular to the ground.[38] All obtained images were exported as TIFF (Tagged Image File Format), 300 dpi, and subsequently imported into the MATLAB R2016a program (The MathWorks, Inc., Natick, Massachusetts, United States). In order to calculate measurement errors, the study reliability was conducted through image evaluation during a 15-day interval. Also, to ensure the double-blind study design, a collaborator who did not evaluate the images performed simple randomization of the images by using computer-generated list of random numbers ("randbetween" function of the Microsoft Excel). The statistician was also blind since he did not know the images groups.

Evaluation of image texture parameters:

Each image was segmented by using the MATLAB Release 2016a program to obtain the following standardized size regions of interest (ROIs) on the mandibular right side, 50X50 pixels (Figure 1): F1 - area delimited in the region of alveolar bone, located between the mental foramen and mandibular cortical bone; M1 – region below and between first and second molars (the center area horizontally 2 cm from the intersection point of the oblique line and ramus in cases with missing right mandibular molars); and R1 - geometric center of mandibular ramus.[32] These ROIs were analyzed using an algorithm based on White and Rudolph[39] study.

Initially, a low-pass filter (Gaussian filter) was applied to reduce the image noise, using the kernel as $e^{\frac{-(x^2+y^2)}{2\sigma^2}} \Big/ 2\pi\sigma^2$ and $\sigma = 35$. Then, the blurred image was subtracted from the original image of each analysed ROI. The resulting image received an additional grey value of 128 and it was made a binary. For this purpose, the Bradley algorithm was used, which considers each pixel of the image to be black if its brightness is k% lower than the average brightness of adjacent pixels.[40] By means of this process, the regions representing the bone trabeculae were evidenced with the black colour and the intertrabecular spaces with the white colour. Afterwards, the resulting image was eroded, dilated and finally skeletonized with the purpose of determining the values of fractal dimension ($d_\int$), lacunarity, and morphological characteristics adopted for the present study.

In order to calculate the fractal dimension, it was used the algorithm of counting cells (box counting), according to the method described by White and Rudolph.[39] The choice of the box-counting method was due to its ease of use in mathematical calculations and experimental measurements. This method considers the ROI covered by a set of squares and, therefore, calculates the number of squares required to cover the entire ROI. The quantity of square is represented by N (s), being "s" the scale, which represents the number of times that the side of the image would be divided. In this context, the calculation of the fractal dimension was done as the following way: $d_\int = \frac{\log N\,(s)}{log\frac{1}{s}}$.

Regarding lacunarity, the medullar region was similarly examined by inverting the image (making the marrow area as black colour) and, then, skeletonizing the resulting image to its core marrow structure.

In addition, some morphological characteristics were obtained from each binary image: 1) trabecular region = total number of black pixels divided by the total number of pixels in the region of interest; 2) periphery = number of pixels at the outer border of the trabeculae, which corresponds to a proportion of the total area of the trabeculae or the total ROI. From the skeletal image, it was obtained: 1) total length of skeletal trabeculae (represented by the total number of black pixels), 2) number of end points (represented by the free ends, that is, each black pixel with only one adjacent black pixel), 3) number of branching points (represented by crossing points, i.e each black pixel with 3 or more adjacent black pixels). These parameters were expressed as a ratio of trabecular length, area, and perimeter.

Bias

As an observational study, the following main factors that could bias the results were avoided[41]: selection and information bias, and measurement error. In order to avoid/minimize the occurrence of selection bias, patients were recruited regardless of the severity of osteometabolic alterations that they might present, and efforts were made to recruit all patients in routine care during the medical outpatient clinic. To avoid / minimize the occurrence of information bias, a detailed anamnesis and careful analysis of the medical records were performed in order to obtain consistent data. To avoid / minimize the occurrence of measurement bias, images were randomized and evaluated in a double-blind design, and it was assessed the reliability of the measurements. In addition, TIFF format was adopted for each image since Yasar et al[42] had found statistically significant difference between TIFF and JPEG images regarding the fractal dimension.

Study size

SSH is a rare disease and its incidence usually range from 0.2 to 2.8 cases per 100,000 women in developed countries.[43] Agarwal et al[12] observed that patients with SSH had a lower bone mineral density in comparison with age- and sex-matched individuals of the control group (0.64 ± 0.09 versus 0.73 ± 0.11). Thus, based on this study, it was considered to evaluate a minimum of 27 patients per study group aiming to obtain a sample with 90% power at a 95% confidence interval. Regarding the possibility of sample loss during the study, 10% was added over the minimum sample calculation previously described, rendering 30 patients per group.

Reliability

To evaluate measurement reliability,[44] the following analyses were performed: (1) intraclass correlation coefficient (ICC) statistics to assess systematic errors related to quantitative variables; (2) Dahlberg's formula to observe random errors of the measurements. Regarding the first one, the bidirectional ICC model of random effects was used with a confidence interval of 95% and a significant level of 5%. To evaluate possible technical errors, the Dahlberg formula was represented as $\sqrt{\frac{\sum d^2}{2n}}$, where $\sum d^2$ is the sum of the squared differences between the two sets of two mean values, and "n" is the number of double measurements.

Statistical methods

Data were statistically analyzed by using the statistical program Statistical Package for the Social Sciences (IBM®, San Diego, CA, USA). Initially, data were submitted to the Kolmogorov-Smirnov normality test and then the results were expressed as the mean and standard deviation (SD) of the mean. All comparisons were performed using the Mann-Whitney test, and a significance level of 5% was adopted.

Results

Regarding the reliability and reproducibility of the panoramic measurements, these errors of measurement were considered acceptable. It was observed an ICC average measure ranging from satisfactory (r = 0.792) to very satisfactory (r = 0.910), and the Dahlberg coefficient ranged from 0.008 to 0.463. Regarding the power of the sample based on the F1 fractal dimension value, comparing individuals in the control group (1.85 ± 0.01) and SSH patients (1.45 ± 0.73), it was statistically estimated an 85.1% power to reject the null hypothesis.

Fractal dimension differed significantly between the studied group. It was observed that its value measured at the region bellow the mental foramen (p = 0.016), region between lower molars (p = 0.043) and center of mandibular ramus (p = 0.028) were statistically lower in the SSH group when compared to the control group (Table 1). Regarding the lacunarity, it was observed that its mean value in mandibular ramus center region (p = 0.008) were statistically higher in SSH group (Table 1).

In relation to morphologic features that characterized the trabeculae, the mean value of Branch points / length measurement ($p = 0.040$) in the mental foramen region was significantly lower in the SSH group (Table 2). In the molar region, the Trabecular area / total area ($p = 0.004$), Periphery / total area ($p = 0.004$), Periphery / Trabecular area ($p = 0.004$), and Length / Trabecular area ($p = 0.029$) were significantly higher in the study group (Table 4). In the central region of the mandibular ramus, Terminal points / cm^2 was statistically higher ($p = 0.036$) in the SSH group when compared to the control group (Table 2).

When the morphological trabecular aspects were compared between the ROIs (Table 3), the region related to the mental foramen showed lower values of Length / trabecular area, Length / total area, Terminal points / cm^2, Terminal points / periphery, Terminal points / trabecular area, Branch points / cm^2, Branch points / periphery, and Branch points / Trabecular area in comparison with the other ROIs ($p < 0.05$). The Branch points / periphery showed a lower value in the region between the molars than in the central region of the mandibular ramus, which was statistically significant ($p < 0.05$).

The cumulative effect of all measurements of trabecular area parameters (Table 4) showed higher values of Trabecular area / total area ($p=0.026$), Periphery / total area ($p=0.026$), Periphery / trabecular area ($p=0.026$), Length / trabecular area ($p=0.018$), Length / total area ($p=0.049$), Terminal points / cm^2 ($p=0.026$), and Branch points / trabecular area ($p=0.008$) in SSH group. The age showed a direct association with lacunarity in mental foramen region ($p=0.035$), as well as Terminal points / periphery ($p = 0.005$) and Branch points / cm^2 ($p = 0.025$) in molar region between SSH individuals. In addition, the Branch points / terminal points ($p = 0.027$) in molar region showed an indirect association with age (Table 5).

Discussion

Several investigations focusing on systemic disorders and its relationships with jawbones sites have performed texture analyses by using fractal dimension investigation in individuals affected by systemic disorders. To date, there are no published studies that evaluated the fractal dimension in SSH, which may reflect the altered bone metabolism in this disease due to pituitary failure.[45]

In SSH, progressive loss of pituitary gland function decreases the secretion of hormones such as growth hormone (GH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (T3 and T4), adrenocorticotrophic hormone (ACTH), cortisol, estradiol, and prolactin. Such hormones may alter the trabecular bone pattern, which may cause osteopenia as well as osteoporosis.[46] Serum levels of LH, FSH, and estradiol are considerably decreased in patients with SSH so that hypogonadism may be one of the possible mechanisms of osteoporosis in these patients. The reduction of GH levels has a significant effect on bone metabolism and plays a crucial role in the maintenance of bone mass in adults, regulating bone remodeling.[5] It is presumed that by reducing the secretion of hormones involved in the regulation of bone metabolism in patients with SSH, the maxillomandibular complex may present varying degrees of osteopenia or even osteoporosis.

The evaluation of bone density in patients with SSH is a relevant topic. However, scarce data has been addressed to the literature, since only 4 studies provided data of bone mass in women affected by this endocrine disease compared with control individuals.[5,12,45,47] Agarwal et al[12] reported 47% of SSH individual with low bone mass (Z-score $\leq$ -2.0) and 48% presenting osteoporosis (T-score $\leq$ 2.5). Chihaoui et al[45] described low bone mineral density in 46 endocrine patients (25 with osteopenia and 21 osteoporosis). Acibucu et al[47] found 61.8% of the patients with osteoporosis and osteopenia in 32.3% of the remaining individuals. Gokalp et al[5] studied premenopausal and postmenopausal SSH patients, and observed lower T- and Z-scores for both femur and spine (L1–L5) compared with controls. The present case-control study could not obtain data about the bone mineral density of the patients, which has been considered a determinant aspect to provide bone strength.[48] However, it was performed in the present study, for the first time in SSH, a mandibular fractal analysis aiming to provide a suitable statistical texture analysis, which reflects the bone texture roughness and grey-level variations.[48] Pothuaud et al[14] demonstrated that fractal analysis of bone texture can distinguish cases with an established diagnosis of osteoporosis from healthy controls.

The present study adopted fractal analysis as a method for estimating mandibular trabecular texture since it represents a mathematical method useful for analysing complex structures such as the trabecular bone.[33,35] It is commonly used to describe the texture roughness and characterize the high degree of complexity of fractal objects by a repetition of self-similarity of the texture grey-level variations over different scales.[36,49] Although the Image J, a freely downloaded programme obtained from the National Institutes of

Health, has been commonly selected as a software to calculate fractal dimension on panoramic radiographs, we processed the images by using MATLAB R2016a to customize a computer program for obtaining measures of fractal dimension, lacunarity and some trabecular architecture morphologic features in panoramic radiographs based on previous studies.[33,39] Also, the present investigation used the box-counting algorithm because it provides the measurement of the trabeculae periphery connectivity.[50]

This investigation used direct digital images for obtaining fractal dimension because some findings support that absence of film processing or imaging digitalization reduces the loss of image information, enhancing the texture parameter measurements reproducibility.[48] In addition, panoramic radiograph was used to assess bone trabecular microarchitecture in SSH because it has been shown as a useful radiographic method for analysing the reduction of bone mineral in the field of maxillofacial imaging, as well as it is a low cost and easy to access exam routinely requested in dentistry.[51]

It has been pointed out that osteoporotic state reduces trabecular complexity and decreases the fractal dimension value.[52] The present results were by this finding since it was obtained a statistically significant difference between SSH and control groups. SSH individuals presented low values of fractal dimension, and this finding agreed with the results of similar investigations that used panoramic radiographs in osteoporotic state-related systemic diseases. Demirbas et al[36] performed fractal analysis on panoramic radiographs of 35 individuals with sickle cell anemia and showed that the value of fractal dimension value in these individuals was significantly lower in comparison to control group. Sindeaux et al[31] found that values of fractal dimension on mandibular cortical bone lower in women with no osteoporosis. Gumussoy et al[35] reported a reduced mean fractal dimension value in a group of 25 patients with chronic renal failure in comparison to healthy individuals. In patients with temporomandibular disorders-related osteoarthritic changes fractal dimension value decreased as the severity of degenerative changes increased, showing that erosive and sclerotic condyles had an altered trabecular pattern.[38]

Data presented in this report support the hypothesis that patients with SSH have an altered trabecular pattern in the mandible, including morphologic aspects obtained from the binary and skeletonized images of the selected regions of interest. It was observed a decrease in the architectural complexity of SSH patients that resembles a similar osteoporotic state as observed in panoramic radiographs of osteoporotic

individuals evaluated by White and Rudolph.[39] SSH individuals showed statistically significant lower values of the trabecular area, periphery, and skeletal length in comparison with the control group, as previously observed in osteoporotic subjects.[39] In this study, the number of terminal points did not differ in comparison with non-SSH patients on the base of the statistical analysis. We believe that this finding may reflect a lower severity of mandibular trabecular alteration presented in this sample of SSH individuals if compared with the results obtained from White and Rudolph[39] study, which highlighted that the number of terminal points is a suitable indicator of bone resorption state in jawbones of osteoporotic patients. Also, the measures of branch points was statistically decreased in SSH, which reflect the core trabecular structure as previously observed.[39] Although some trabeculae morphologic features did not show the statistically significant difference in SSH group, even decreased in comparison with control group, this finding was observed in a group of post-menopausal women with low bone mineral density assessed by DXA.[53]

Presently, the diagnosis delay found among the individuals with SSH was 11.81 ± 8.95 years. This finding was similar to the data presented by Ramiandrasoa et al[54] since they described a mean delay of 9 ± 9.7 years in a sample of 39 women diagnosed with SSH. Stockholm et al[55] support the hypothesis that this diagnosis delay occur because SSH is a chronic disease. In this context, we also believe that the lower fractal dimension values and altered morphologic features observed in this investigation probably were a consequence of the negative effect of a delayed diagnosis on the bone mass content loss over the years and the socio-economic position that could influence in a nutritional deficit. Bone mineral density has been compromised in SSH because these patients usually are diagnosed with hypopituitarism at young age, and they develop important nutritional deficiency,[56] which is significant affected by the socio-economic status-related risk factors, including calcium, protein and vitamin D intake.[57] This finding was previously discussed by our group in an observational study with SSH individuals, and it was showed a remarkable lower socio-economic strata.[58]

Based on the findings of the present novel research, the SSH sample studied was characterized by a decrease in fractal dimension and some morphologic features, which may be a reflect of a possible reduced bone mineral density in these individuals due to osteometabolic changes that occurred over the years since the onset of the systemic manifestations associated with the postpartum hemorrhage. We believe fractal analysis

may be an alternative and useful tool for improving the diagnostic capacity of panoramic radiography on mandibular changes of individuals with SSH. Also, it is necessary further SSH studies in the field of the maxillofacial imaginology, especially those correlating bone texture aspects and bone mineral density by dual energy x-ray absorptiometry.

References

1. Imam A, Iqbal J, Blair HC, Davies TF, Huang CL, Zallone A, Zaidi M, Sun L. Role of the pituitary-bone axis in skeletal pathophysiology. Curr Opin Endocrinol Diabetes Obes. 2009 Dec;16(6):423-9. doi: 10.1097/MED.0b013e3283328aee.

2. Colaianni G, Cuscito C, Colucci S. FSH and TSH in the regulation of bone mass: the pituitary/immune/bone axis. Clin Dev Immunol. 2013;2013:382698. doi: 10.1155/2013/382698.

3. Zaidi M, Sun L, Liu P, Davies TF, New M, Zallone A, Yuen T. Pituitary-bone connection in skeletal regulation. Horm Mol Biol Clin Investig. 2016 Nov 1;28(2):85-94. doi: 10.1515/hmbci-2016-0015.

4. Sheehan HL. Postpartum necrosis of the anterior pituitary. J. Pathol Bact. 1937;45:189–214.

5. Gokalp D, Tuzcu A, Bahceci M, Arikan S, Ozmen CA, Cil T. Sheehan's syndrome and its impact on bone mineral density. Gynecol Endocrinol. 2009 May;25(5):344-9.

6. Karaca Z, Laway BA, Dokmetas HS, Atmaca H, Kelestimur F. Sheehan syndrome. Nat Rev Dis Primers. 2016 Dec 22;2:16092. doi: 10.1038/nrdp.2016.92.

7. Haddock L, Vega LA, Aguil ´o F, Rodriguez O. Adrenocortical, thyroidal and human growth hormone reserve in Sheehan’s syndrome. Johns Hopkins Med Bull 1972;131:80–99.

8. Keleştimur F. Sheehan's syndrome. Pituitary. 2003;6(4):181-8.

9. Sert M, Tetiker T, Kirim S, Kocak M. Clinical report of 28 patients with Sheehan's syndrome. Endocr J. 2003;50:297-301.

10. Dökmetaş HS, Kilicli F, Korkmaz S. Yonem O. Characteristic features of 20 patients with Sheehan's syndrome. Gynecol Endocrinol. 2006;22:279-83.

11. Diri H, Tanriverdi F, Karaca Z, Senol S, Unluhizarci K, Durak AC, Atmaca H, Kelestimur F. Extensive investigation of 114 patients with Sheehan's syndrome: a continuing disorder. Eur J Endocrinol. 2014 Sep;171(3):311-8. doi: 10.1530/EJE-14-0244.

12. Agarwal P, Gomez R, Bhatia E, Yadav S. Decreased bone mineral density in women with Sheehan's syndrome and improvement following oestrogen replacement and nutritional supplementation. J Bone Miner Metab. 2018 Feb 20. doi: 10.1007/s00774-018-0911-6.

13. Grampp S, Genant HK, Mathur A, Lang P, Jergas M, Takada M, Glüer CC, Lu Y, Chavez M. Comparisons of noninvasive bone mineral measurements in assessing age-related loss, fracture discrimination, and diagnostic classification. J Bone Miner Res. 1997 May;12(5):697-711.

14. Pothuaud L, Lespessailles E, Harba R, Jennane R, Royant V, Eynard E, Benhamou CL. Fractal analysis of trabecular bone texture on radiographs: discriminant value in postmenopausal osteoporosis. Osteoporos Int. 1998;8(6):618-25.

15. Geraets WGM, Van der Stelt PF, Elders PJM. The radiographic trabecular bone pattern during menopause. Bone 1993;14:859–64.

16. Muller R, Hilde brand T, Hauselmann HJ, Ruegsegger P. In vivo reproducibility of three-dimensional structural properties of non-invasive bone biopsy using 3D-mQCT. J Bone Miner Res 1996;11:1745–50.

17. Roberts MG, Graham J, Devlin H. Image texture in dental panoramic radiographs as a potential biomarker of osteoporosis. IEEE Trans Biomed Eng. 2013 Sep;60(9):2384-92. doi: 10.1109/TBME.2013.2256908

18. Arsan B, Köse TE, Çene E, Özcan İ. 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 Mar;123(3):382-391. doi: 10.1016/j.oooo.2016.11.005.

19. Kavitha MS, Ganesh Kumar P, Park SY, Huh KH, Heo MS, Kurita T, Asano A, An SY, Chien SI. Automatic detection of osteoporosis based on hybrid genetic swarm fuzzy classifier approaches. Dentomaxillofac Radiol. 2016;45(7):20160076. doi: 10.1259/dmfr.20160076.

20. Ling H, Yang X, Li P, Megalooikonomou V, Xu Y, Yang J. Cross gender-age trabecular texture analysis in cone beam CT. Dentomaxillofac Radiol. 2014;43(4):20130324. doi: 10.1259/dmfr.20130324.

21. Servais JA, Gaalaas L, Lunos S, Beiraghi S, Larson BE, Leon-Salazar V. Alternative cone-beam computed tomography method for the analysis of bone density around impacted maxillary canines. Am J Orthod Dentofacial Orthop. 2018 Sep;154(3):442-449. doi: 10.1016/j.ajodo.2018.01.008.

22. Shrout MK, Hildebolt CF, Potter BJ. The effect of varying the region of interest on calculations of fractal index. Dentomaxillofac Radiol. 1997 Sep;26(5):295-8.

23. Chen SK, Chen CM. The effects of projection geometry and trabecular texture on estimated fractal dimensions in two alveolar bone models. Dentomaxillofac Radiol. 1998 Sep;27(5):270-4.

24. Lee KI, Choi SC, Park TW, You DS. Fractal dimension calculated from two types of region of interest. Dentomaxillofac Radiol. 1999 Sep;28(5):284-9.

25. Geraets WG, van der Stelt PF. Fractal properties of bone. Dentomaxillofac Radiol. 2000 May;29(3):144-53. Review.

26. Bollen AM, Taguchi A, Hujoel PP, Hollender LG. Fractal dimension on dental radiographs. Dentomaxillofac Radiol. 2001 Sep;30(5):270-5.

27. Pornprasertsuk S, Ludlow JB, Webber RL, Tyndall DA, Yamauchi M. Analysis of fractal dimensions of rat bones from film and digital images. Dentomaxillofac Radiol. 2001 May;30(3):179-83.

28. Yasar F, Akgünlü F. Fractal dimension and lacunarity analysis of dental radiographs. Dentomaxillofac Radiol. 2005 Sep;34(5):261-7.

29. Jolley L, Majumdar S, Kapila S. Technical factors in fractal analysis of periapical radiographs. Dentomaxillofac Radiol. 2006 Nov;35(6):393-7.

30. Yaşar F, Akgünlü F. The differences in panoramic mandibular indices and fractal dimension between patients with and without spinal osteoporosis. Dentomaxillofac Radiol. 2006 Jan;35(1):1-9.

31. Sindeaux R, Figueiredo PT, de Melo NS, Guimarães AT, Lazarte L, Pereira FB, de Paula AP, Leite AF. Fractal dimension and mandibular cortical width in normal and osteoporotic men and women. Maturitas. 2014 Feb;77(2):142-8. doi: 10.1016/j.maturitas.2013.10.011.

32. Hwang JJ, Lee JH, Han SS, Kim YH, Jeong HG, Choi YJ, Park W. Strut analysis for osteoporosis detection model using dental panoramic radiography. Dentomaxillofac Radiol. 2017 Oct;46(7):20170006. doi: 10.1259/dmfr.20170006.

33. Apolinário AC, Sindeaux R, de Souza Figueiredo PT, Guimarães AT, Acevedo AC, Castro LC, de Paula AP, de Paula LM, de Melo NS, Leite AF. Dental panoramic indices and fractal dimension measurements in osteogenesis imperfecta children under pamidronate treatment. Dentomaxillofac Radiol. 2016;45(4):20150400. doi: 10.1259/dmfr.20150400.

34. Ergün S, Saraçoglu A, Güneri P, Ozpinar B. Application of fractal analysis in hyperparathyroidism. Dentomaxillofac Radiol. 2009 Jul;38(5):281-8. doi: 10.1259/dmfr/24986192.

35. 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(5):20150389. doi: 10.1259/dmfr.20150389.

36. Demirbaş AK, Ergün S, Güneri P, Aktener BO, Boyacioğlu H. Mandibular boné changes in sickle cell anemia: fractal analysis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008 Jul;106(1):e41-8. doi: 10.1016/j.tripleo.2008.03.007.

37. 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 Aug;126(2):184-191. doi: 10.1016/j.oooo.2018.04.010.

38. Rondon RH, Pereira YC, do Nascimento GC. Common positioning errors in panoramic radiography: A review. Imaging Sci Dent. 2014 Mar;44(1):1-6. doi: 10.5624/isd.2014.44.1.1.

39. 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 Nov;88(5):628-35.

40. Bradley D, Roth, G. Adaptative thresholding using the integral image. Journal of Graphics Tools 2007; 12: 13 – 21.

41. Hammer GP, du Prel JB, Blettner M. Avoiding bias in observational studies: part 8 in a series of articles on evaluation of scientific publications. Dtsch Arztebl Int. 2009 Oct;106(41):664-8. doi: 10.3238/arztebl.2009.0664.

42. Yasar F, Apaydin B, Yilmaz HH. The effects of image compression on quantitative measurements of digital panoramic radiographs. Med Oral Patol Oral Cir Bucal. 2012 Nov 1;17(6):e1074-81.

43. Kovacs K. Sheehan syndrome. Lancet. 2003;361:520-2.

44. Harris EF, Smith RN. Accounting for measurement error: a critical but often overlooked process. Arch Oral Biol. 2009 Dec;54 Suppl 1:S107-17. doi: 10.1016/j.archoralbio.2008.04.010.

45. Chihaoui M, Yazidi M, Chaker F, Belouidhnine M, Kanoun F, Lamine F, Ftouhi B, Sahli H, Slimane H. Bone Mineral Density in Sheehan's Syndrome; Prevalence of Low Bone Mass and Associated Factors. J Clin Densitom. 2016 Oct;19(4):413-418. doi: 10.1016/j.jocd.2016.02.002.

46. Bolanowski M, Halupczok J, Jawiarczyk-Przybyłowska A. Pituitary disorders and osteoporosis. Int J Endocrinol. 2015;2015:206853. doi: 10.1155/2015/206853.

47. Acibucu F, Kilicli F, Dokmetas HS. Assessment of bone mineral density in patients with Sheehan's syndrome. Gynecol Endocrinol. 2014 Jul;30(7):532-5. doi: 10.3109/09513590.2014.900033.

48. Lespessailles E, Gadois C, Lemineur G, Do-Huu JP, Benhamou L. Bone texture analysis on direct digital radiographic images: precision study and relationship with bone mineral density at the os calcis. Calcif Tissue Int. 2007 Feb;80(2):97-102.

49. Benhamou CL, Lespessailles E, Jacquet G, Harba R, Jennane R, Loussot T, Tourliere D, Ohley W. Fractal organization of trabecular bone images on calcaneus radiographs. J Bone Miner Res. 1994 Dec;9(12):1909-18.

50. Yu YY, Chen H, Lin CH, Chen CM, Oviir T, Chen SK, Hollender L. Fractal dimension analysis of periapical reactive bone in response to root canal treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009 Feb;107(2):283-8. doi: 10.1016/j.tripleo.2008.05.047.

51. Lee BD, White SC. Age and trabecular features of alveolar bone associated with osteoporosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005 Jul;100(1):92-8.

52. Updike SX, Nowzari H. Fractal analysis of dental radiographs to detect periodontitis-induced trabecular changes. J Periodontal Res 2008; 43: 658–64. doi: http://dx.doi.org/10.1111/j.1600-0765.

53. Licks R, Licks V, Ourique F, Radke Bittencourt H, Fontanella V. Development of a prediction tool for low bone mass based on clinical data and periapical radiography. Dentomaxillofac Radiol. 2010 May;39(4):224-30. doi: 10.1259/dmfr/23760876.

54. Ramiandrasoa C, Castinetti F, Raingeard I, Fenichel P, Chabre O, Brue T, Courbière B. Delayed diagnosis of Sheehan's syndrome in a developed country: a retrospective cohort study. Eur J Endocrinol. 2013 Sep 12;169(4):431-8. doi: 10.1530/EJE-13-0279.

55. Stochholm K, Gravholt CH, Laursen T, Laurberg P, Andersen M, Kristensen LØ, Feldt-Rasmussen U, Christiansen JS, Frydenberg M, Green A. Mortality and GH deficiency: a nationwide study. Eur J Endocrinol. 2007 Jul;157(1):9-18.

56. Zargar AH, Singh B, Laway BA, Masoodi SR, Wani AI, Bashir MI. Epidemiologic aspects of postpartum pituitary hypofunction (Sheehan's syndrome). Fertil Steril. 2005 Aug;84(2):523-8.

57. Shatrugna V, Kulkarni B, Kumar PA, Rani KU, Balakrishna N. Bone status of Indian women from a low-income group and its relationship to the nutritional status. Osteoporos Int. 2005 Dec;16(12):1827-35.

58. Cavalcante DD, Pinto-Quidute AR, Alves-Martins MR, Walter-de-Aguiar AS, Lima-Cid AM, Silva PG, Cavalcante RF, Costa FW. Dental status, salivary flow, and sociodemographic aspects in Sheehan Syndrome patients. Med Oral Patol Oral Cir Bucal. 2018 Jul 1;23(4):e436-e442.

Tables

Table 1. Fractal dimension and lacunarity values.

ROI	Parameters	Group		
		Control	SSH	p-Value
Region between the mental foramen and mandibular cortical bone (F1)	Fractal dimension	1.85±0.01	1.47±0.72	0.016*
	Lacunarity	0.90±0.33	0.85±0.37	0.740
Region between first and second molars (M1)	Fractal dimension	1.68±0.51	1.52±0.67	0.043*
	Lacunarity	0.99±0.17	0.96±0.32	0.220
Geometric center of mandibular ramus (R1)	Fractal dimension	1.74±0.42	1.68±0.50	0.028*
	Lacunarity	0.90±0.32	0.97±0.23	0.008*

ROI, region of interest; *p<0.05; Mann-Whitney test (mean±SD).

Table 2. Morphological features related to the trabecular bone.

	F1			M1			R1		
	Control	**SSH**	**p-Value**	**Control**	**SSH**	**p-Value**	**Control**	**SSH**	**p-Value**
Trabecular area / total area	0.58±0.04	0.57±0.04	0.537	0.60±0.05	0.57±0.03	0.004*	0.60±0.06	0.58±0.04	0.130
Periphery / total area	0.42±0.04	0.43±0.04	0.537	0.40±0.05	0.43±0.03	0.004*	0.40±0.06	0.42±0.04	0.130
Periphery / trabecular area	0.72±0.13	0.75±0.11	0.679	0.66±0.13	0.75±0.09	0.004*	0.68±0.15	0.73±0.11	0.138
Lenght / trabecular area	0.27±0.05	0.29±0.03	0.259	0.29±0.06	0.32±0.03	0.029*	0.30±0.06	0.32±0.04	0.080
Lenght / total area	0.16±0.02	0.16±0.01	0.204	0.17±0.02	0.18±0.02	0.243	0.17±0.02	0.18±0.02	0.052
Terminal points / cm^2	0.12±0.02	0.12±0.01	0.557	0.13±0.02	0.14±0.02	0.286	0.13±0.02	0.14±0.02	0.036*
Terminal points / lenght	0.76±0.03	0.76±0.05	0.835	0.75±0.04	0.76±0.04	0.795	0.76±0.04	0.78±0.04	0.129
Terminal points / periphery	0.29±0.04	0.29±0.03	0.755	0.33±0.04	0.32±0.03	0.528	0.33±0.03	0.34±0.03	0.354
Terminal points / trabecular area	0.21±0.05	0.22±0.04	0.463	0.22±0.05	0.24±0.03	0.068	0.23±0.05	0.25±0.04	0.064
Branch points / cm^2	0.15±0.02	0.16±0.01	0.491	0.17±0.02	0.17±0.02	0.256	0.17±0.02	0.18±0.02	0.068
Branchs points / lenght	0.97±0.01	0.96±0.01	0.040*	0.97±0.02	0.97±0.01	0.256	0.97±0.01	0.97±0.01	0.611
Branch points / periphery	0.36±0.04	0.37±0.04	0.749	0.42±0.05	0.41±0.04	0.265	0.42±0.03	0.42±0.04	0.766
Branch points / trabecular area	0.26±0.05	0.28±0.04	0.354	0.28±0.05	0.31±0.03	0.032	0.29±0.06	0.31±0.04	0.106
Branch points / terminal points	1.16±0.36	1.12±0.40	0.705	1.14±0.41	1.19±0.31	0.756	1.23±0.22	1.13±0.36	0.184

*$p<0.05$; Mann-Whitney test (mean±SD).

Table 3. Comparison of texture imaging parameters between the ROIs.

	F1 x M1	p-Value	F1 x R1	p-Value	M1 x R1	p-Value
Fractal dimension	NS	0.107	NS	0.136	NS	0.975
Lacunarity	F1 < M1	0.019*	F1 > R1	<0.001*	M1 > R1	0.018*
Trabecular area / total area	NS	0.693	NS	0.455	NS	0.250
Periphery / total area	NS	0.693	NS	0.455	NS	0.250
Periphery / trabecular area	NS	0.940	F1 < R1	0.673	NS	0.172
Lenght / trabecular area	F1 < M1	0.001*	F1 < R1	0.001*	NS	0.444
Lenght / total area	F1 < M1	<0.001*	F1 < R1	<0.001*	NS	0.075
Terminal points / cm^2	F1 < M1	0.003*	F1 < R1	<0.001*	NS	0.146
Terminal points / lenght	F1 = M1	0.656	NS	0.117	NS	0.144
Terminal points / periphery	F1 < M1	0.002*	F1 < R1	<0.001*	M1 < R1	0.015*
Terminal points / trabecular area	F1 < M1	0.029*	F1 < R1	0.002*	NS	0.221
Branch points / cm^2	F1 < M1	<0.001*	F1 < R1	<0.001*	NS	0.467
Branchs points / lenght	NS	0.158	NS	0.973	NS	0.206
Branch points / periphery	F1 < M1	<0.001*	F1 < R1	<0.001*	NS	0.052
Branch points / trabecular area	F1 < M1	0.002*	F1 < R1	0.001*	NS	0.549
Branch points / terminal points	NS	0.683	NS	0.315	NS	0.374

*$p<0.05$; Wilcoxon test (mean±SD).

Table 4. Cumulative effect of the morphological features related to the trabecular bone between the studied groups.

	Group		
	Control	**SSH**	**p-Value**
Trabecular area / total area	0.59±0.04	0.57±0.03	0.026*
Periphery / total area	0.41±0.04	0.43±0.03	0.026*
Periphery / trabecular area	0.69±0.11	0.74±0.08	0.035*
Lenght / trabecular area	0.28±0.05	0.31±0.03	0.018*
Lenght / total area	0.17±0.02	0.18±0.01	0.049*
Terminal points / cm^2	0.13±0.02	0.13±0.01	0.089
Terminal points / lenght	0.76±0.03	0.77±0.03	0.256
Terminal points / periphery	0.31±0.02	0.32±0.02	0.747
Terminal points / trabecular area	0.22±0.04	0.24±0.03	0.060
Branch points / cm^2	0.16±0.02	0.17±0.01	0.067
Branchs points / lenght	0.97±0.01	0.97±0.01	1.000
Branch points / periphery	0.40±0.02	0.40±0.03	0.756
Branch points / trabecular area	0.27±0.05	0.30±0.03	0.026*
Branch points / terminal points	1.18±0.21	1.15±0.21	0.613

*$p<0.05$; Mann-Whitney test (mean±SD).

Table 5. Texture imaging parameters according to age groups.

	F1			M1			R1		
	Up to 65	**>65**	**p-Value**	**Up to 65**	**>65**	**p-Value**	**Up to 65**	**>65**	**p-Value**
Fractal Dimension	1.71±0.51	1.34±0.80	0.173	1.33±0.80	1.71±0.46	0.154	1.71±0.46	1.59±0.62	0.558
Lacunarity	0.67±0.47	0.95±0.26	0.035*	0.88±0.35	0.88±0.36	0.970	1.03±0.00	0.96±0.26	0.334
Trabecular area / total area	0.56±0.04	0.57±0.05	0.649	0.57±0.04	0.57±0.02	1.000	0.58±0.05	0.58±0.03	0.616
Periphery / total area	0.44±0.04	0.43±0.05	0.649	0.43±0.04	0.43±0.02	1.000	0.42±0.05	0.42±0.03	0.616
Periphery / trabecular area	0.76±0.10	0.74±0.12	0.633	0.75±0.11	0.75±0.07	0.967	0.72±0.15	0.74±0.09	0.711
Lenght / trabecular area	0.29±0.03	0.28±0.04	0.508	0.30±0.04	0.32±0.02	0.142	0.32±0.06	0.32±0.03	0.934
Lenght / total area	0.17±0.01	0.16±0.01	0.334	0.17±0.02	0.18±0.01	0.084	0.19±0.02	0.19±0.01	0.914
Terminal points / cm^2	0.13±0.01	0.12±0.01	0.408	0.13±0.02	0.14±0.01	0.008*	0.14±0.02	0.14±0.02	0.849
Terminal points / lenght	0.77±0.04	0.76±0.06	0.632	0.74±0.05	0.78±0.02	0.019*	0.78±0.05	0.77±0.03	0.795
Terminal points / periphery	0.29±0.03	0.29±0.03	0.704	0.30±0.04	0.34±0.01	0.005*	0.35±0.04	0.34±0.03	0.497
Terminal points / trabecular area	0.23±0.03	0.22±0.04	0.414	0.23±0.04	0.25±0.02	0.069	0.25±0.06	0.25±0.03	0.968
Branch points / cm^2	0.16±0.01	0.16±0.01	0.623	0.17±0.02	0.18±0.01	0.025*	0.18±0.02	0.18±0.01	0.917
Branchs points / lenght	0.97±0.01	0.96±0.01	0.381	0.97±0.01	0.97±0.01	0.292	0.97±0.02	0.97±0.01	1.000
Branch points / periphery	0.37±0.03	0.36±0.04	0.866	0.40±0.04	0.42±0.02	0.102	0.43±0.04	0.42±0.03	0.328
Branch points / trabecular area	0.28±0.04	0.27±0.04	0.395	0.30±0.04	0.31±0.02	0.237	0.31±0.06	0.31±0.03	0.934
Branch points / terminal points	1.17±0.32	1.10±0.44	0.632	1.31±0.08	1.24±0.04	0.027*	1.16±0.32	1.07±0.44	0.538

*$p<0.05$; Mann-Whitney test (mean±SD).