RESEARCH ARTICLE

Dental panoramic indices and fractal dimension measurements in osteogenesis imperfecta children under pamidronate treatment

¹Ana C Apolinário, ¹Rafael Sindeaux, ²Paulo T de Souza Figueiredo, ³Ana T B Guimarães, ⁴Ana C Acevedo, ⁵Luiz C Castro, ⁶Ana P de Paula, ⁴Lilian M de Paula, ⁷Nilce S de Melo and ²André F Leite

¹Department of Dentistry, University of Brasília, Campus Universitário Darcy Ribeiro, Asa Norte, Brazil; ²Department of Rheumatology, Oral Radiology, Department of Dentistry, Faculty of Health Science, University of Brasília, Campus Universitário Darcy Ribeiro, Brazil; ³Biological Sciences Department, State University of West Paraná, Rua Universitária, Cascavel, Paraná, Brazil; ⁴Oral Care Center for Inherited Diseases, Department of Dentistry, Faculty of Health Science, University of Brasília, Campus Universitário Darcy Ribeiro, Brazil; ⁵Division of Endocrinology, University of Brasília's Hospital, Brasília, Brazil; ⁶Hospital de Base of Federal District, Brasília, Brazil; ⁷Oral Pathology, Department of Dentistry, Faculty of Health Science, University of Brasília, Campus Universitário Darcy Ribeiro Asa Norte, Brazil

Objectives: To verify radiomorphometric indices and fractal dimension (FD) in dental panoramic radiographs (DPRs) of children with different types of osteogenesis imperfecta (OI) and also to verify the effect of pamidronate (PAM) treatment in such panoramic analyses.

Methods: In this retrospective study, 197 DPRs of 62 children with OI Types I, III and IV who were in treatment with a comparable dosage of intravenous PAM were selected. The mandibular cortical width (MCW), mandibular cortical index, visual estimation of the cortical width and FD of three standardized trabecular and cortical mandibular regions of interest were obtained from the radiographs. Factorial analysis of variance and Fisher test were used to compare FD and MCW measurements in children with different types of OI for different PAM cycles.

Results: Children with all types of OI have thinner and more porous mandibular cortices at the beginning of treatment. There were significant differences between MCW and FD of the cortical bone, regarding different types of OI and number of PAM cycles ($p = 0.037$ and $p = 0.044$, respectively). FD measurements of the trabecular bone were not statistically different among OI types nor were PAM cycles ($p > 0.05$).

Conclusions: Children with OI presented cortical bone alterations after PAM treatment. Both MCW and the FD of the cortical bone were higher in children with OI after PAM treatment. It is argued that cortical bone should be considered for analyzing patients with OI, as well as to monitor the progress of PAM treatment.

Dentomaxillofacial Radiology (2016) **45**, 20150400. doi: 10.1259/dmfr.20150400

Cite this article as: Apolinário AC, Sindeaux R, Figueiredo PT, Guimarães ATB, 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.

Keywords: panoramic radiography; bone disease; fractals; diphosphonate

Introduction

Osteogenesis imperfecta (OI) is an inherited heterogeneous connective tissue disorder characterized by

several degrees of low bone mass and increased susceptibility to fractures. The majority of the cases are autosomal dominant forms with mutations in the *COL1A1* or *COL1A2* genes encoding the alpha chains of Type I collagen. The clinical severity varies widely from

Correspondence to: Dr André Ferreira Leite. E-mail: andreleite@unb.br;

Received 27 November 2015; revised 3 March 2016; accepted 7 March 2016

nearly asymptomatic with a mild predisposition to fractures to profoundly disabling and even lethal.¹ The original classification proposed four OI types based on clinical/radiological features and inheritance.² Since then, other types, mainly autosomal recessive forms, have been ascertained, based on the identification of different mutations and histological findings.^{3–6} Several manifestations can be associated with OI, such as blue sclera, dentinogenesis imperfecta, hyperlaxity of ligaments and skin, hearing impairment and the presence of Wormian bones on skull radiographs. The most relevant clinical characteristic of this disorder is bone fragility, and its severity increases in the following order, based on the original classification of the disease: Type I < Type IV < Type III < Type II. The purpose of OI treatment is to maximize mobility and daily life competencies and to decrease bone pain and bone fragility. Handling should be multidisciplinary and includes rehabilitation, and surgical and pharmacological treatment.^{7–9}

The cyclic administration of intravenous pamidronate (PAM), which is the bisphosphonate most used for patients with OI, inhibits the function of osteoclasts. Therefore, this pharmacological treatment has shown to reduce bone resorption, increase bone mass and decrease fracture rate.¹⁰ A trans-iliac histomorphometric study after PAM therapy showed that cortical width increased by 88%. On the other hand, the trabecular thickness did not change significantly. The cancellous bone volume increased by 46%. This increasing of the cancellous bone was due to a higher trabecular number without an effect on trabecular thickness.¹¹

A number of mandibular indices based on panoramic radiographs and image processing and analysis techniques have been developed to allow quantification of mandibular bone mass and trabecular microarchitecture in order to predict skeletal low bone mineral density (BMD) in elderly patients.^{12–29} Several studies^{13,14,17} have demonstrated that patients with osteoporosis present lower mandibular cortical width (MCW) values. Some authors^{16,17,20} have verified erosion of the mandibular cortex in patients with low BMD, by using qualitative and visual indices, such as mandibular cortical index (MCI) and the visual estimation of the cortical width (SVE). The bone microarchitecture is deteriorated in patients with osteoporosis; the thickness and the number of trabeculae are diminished; and the trabeculae are more separated. Thus, changes in bone microarchitecture caused by osteoporosis alter X-ray attenuation and thereby modify the density and texture of the image.³⁰ Another technique that has been used to measure mandibular bone mass and trabecular architecture is fractal dimension (FD) analysis which is a mathematical technique that can aid in the quantification of complex structures.²⁸

Although dental panoramic radiographs (DPRs) are widely used in dental practice, the cortical indices and FD have yet to be studied in paediatric patients. Childhood and adolescence are periods of high skeletal growth when >90% of adult bone mass is acquired. The

optimization of peak bone mass acquisition and strength at an early age appears to have an important significance in the prevention of osteoporosis and fractures in the elderly.³¹ Several conditions can lead to low BMD in children, such as reduced mobility, decreased growth rate, inadequate nutrition, use of anti-convulsants, low vitamin D levels, irregularities in pubertal and skeletal maturation and genetic disorders that affect bone acquisition and turnover.³² Children with OI have low BMD.³³ Through PAM cycles, bone mass, size and BMD increase substantially when compared with non-treated subjects. Although BMD seems to be an indicator of OI severity, the available densitometric evidence is limited for these patients because of difficulties in interpretation of results due to the small size of their bones, deformities, vertebral compression fractures, scoliosis and a history of prolonged immobilization. Despite difficulties, BMD increases during PAM treatment.³⁴ Furthermore, the effect of PAM treatment on the mandibular cortex of patients with OI was verified in one recent study.³⁵

The aim of this study was to verify radiomorphometric indices and FD in DPRs of children with different types of OI and to also verify the effect of PAM in such DPRs analyses. The hypothesis is that the thinning and resorption of mandibular cortical and trabecular bone is higher at the beginning of treatment. Through PAM cycles, an increase in quality and width might occur. Then, dental panoramic measurements could be used to analyze children with OI with low BMD and also the treatment effect on the cortical and trabecular bones.

Methods and materials

The Research Ethics Committee of the University of Brasília, Brazil, approved this study, and informed consents were obtained from all individuals. This was a retrospective radiographic study based on DPR images collected from an existing database of 105 children with OI from the University Hospital of Brasília, Brasília, Brazil. The disease (OI) diagnosis was made by the Pediatric Endocrinology Center at the same hospital. All patients were referred for dental treatment and follow-up at the Oral Care Center for Inherited Diseases of this hospital. They were also under medical treatment with PAM.

To be included in the study, the children should have DPRs performed that meet the technical quality criteria. The mandibular cortex should be completely visible. Subjects with other metabolic diseases were excluded. From the original database, 43 patients were excluded from the final sample (10 did not have DPRs, 9 did not match the DPR quality criteria, 9 were adults, 3 were babies, 1 had other metabolic disease, and in 11 patients, OI diagnosis was not confirmed). The final sample consisted of 197 DPRs of 62 selected children with OI Types I, III and IV who had been treated with cyclic PAM between 2007 and 2012. As OI Type II is usually lethal at early age, no patient with this disease type was included

Figure 1 (a–c) Graphic and radiographic representation of mandibular cortical index evaluation in osteogenesis imperfecta patients. C1, the endosteal margin of the cortex was even and sharp; C2, the endosteal margin presented semi-lunar defects (lacunar resorption) or appeared to form endosteal cortical residues; or C3, the cortical layer formed heavy endosteal cortical residues and was clearly porous.

in the final sample. Furthermore, during the period of the study, patients with OI Types V, VI, VII and VIII had not been diagnosed in our hospital.

PAM was administered at 4-month intervals on 2 or 3 consecutive days to children over 3 years old, in a dosage of $1.0 \text{ mg kg}^{-1} \text{ day}^{-1}$ for the 3 days cycle; for the 2 days scheme, the dosage was $1.5 \text{ mg kg}^{-1} \text{ day}^{-1}$, and the annual cumulative dosage was 9 mg kg^{-1} . This was an established treatment protocol designed for children with OI at our institution.

All radiographs were taken using the same panoramic machine (Rotograph Plus; Villa Sistemi Medicali, Buccinasco, Milan, Italy) at 10 mA and 15 s; the voltage varied between 60 and 75 kV. Patients were positioned in the dental panoramic machine in such a way that the vertical line produced by the machine was aligned with the patient's sagittal plane, with the horizontal line (Frankfort plane) parallel to the floor. The radiographs were taken at different times during the PAM cycle.

All radiographs were scanned in 8-bit greyscale acquisition depth and 300 dpi spatial resolutions, with a scanner with the transparency adaptor Epson Expression, 1680Pro (Seiko Epson Corp., Nagano, Japan). Images were stored in JPEG format with a matrix of 3188×1709 pixels (the image file size was 5.20 Mb and each pixel was about $84 \times 10^{-4} \text{ mm}^2$) and 256 grey levels. For measuring radiomorphometric indices and the FD, the digitized panoramic images were analyzed by an experienced professional using ImageJ v. 1.45s software (National Institutes of Health, Bethesda, MD), which is a public domain program that can be downloaded from the world wide web (<http://rsb.info.nih.gov/ij/download.html>).

Radiomorphometric indices

The radiomorphometric indices were evaluated according to previous studies with osteoporotic adults.^{12,13,16} In this way, two qualitative indices (SVE and MCI) and one quantitative index (MCW) were analyzed, as follows:

SVE: the cortex was classified into two categories based on simple visual estimation of mandibular inferior cortex widths: thin and not thin.¹⁶

MCI: the appearance of the inferior cortex of the mandible was classified as: C1, the endosteal margin of the cortex was even and sharp; C2, the endosteal margin presented semi-lunar defects (lacunar resorption) or appeared to form endosteal cortical residues; or C3, the cortical layer formed heavy endosteal cortical residues and was clearly porous (Figure 1).¹²

MCW: a line parallel to the long axis of the mandible and tangential to the inferior border of the mandible was drawn. A line perpendicular to this tangent intersecting the inferior border of the mental foramen was constructed, along which MCW was measured.¹³

Fractal dimension measurements

For FD analysis, three regions of interest (ROIs) were selected on the right side of the panoramic images (Figure 2), two from the trabecular and one from the cortical bone, as follows: ROI 1: a square of 25×25 pixels in the trabecular bone, in the geometric centre of the mandibular ramus; ROI 2: a square of 25×25 pixels in the trabecular bone, in the geometric centre of the mandibular angle; and ROI 3: a rectangle in the basal cortical bone, distal to the mental foramen extending to the distal root of the first permanent molar. This procedure was

Figure 2 Processing of panoramic radiograph for fractal dimension calculation after selecting the regions of interest (ROIs). (a) Panoramic radiograph with the three selected ROIs (1, 2 and 3), two from the trabecular bone and one from the cortical bone; (b) the original selected ROI on the cortical bone; (c) a gaussian blurred image; (d) a subtraction image; (e) an added 128 image; (f) a binary image; (g) an eroded image; (h) a dilated image; (i) a skeletonized image; (j) the box counting procedure.

carried out so that only the mandibular cortex was included in the selected ROI. The third ROI was selected by using the polygon tool of the ImageJ software.

The saved images were processed following the method used in several previous studies.^{23–25} Figure 2 shows the sequence of procedures to calculate FD in DPRs of a child with OI. First, the ROI was selected, cropped and duplicated. Then, the duplicated image was blurred with a gaussian filter (sigma, 35) to remove large-scale variations in brightness on the image. The blurred image was subtracted from the original ROI image and a gray value of 128 was added at each pixel location. The

resultant image was then made binary and, with this process, the regions that represent the trabecular bone were set to white, and marrow spaces were set to black. The image was eroded and dilated to reduce the noise. After dilation, the image was skeletonized and was used for fractal analysis. The FD was calculated by the box-counting method. The widths of the square boxes were 2, 3, 4, 6, 8, 12, 16, 32 and 64 pixels.

Statistical analysis

Calculations of mean and standard deviation were performed for the quantitative variables, and the absolute

Table 1 Number of panoramic radiographs taken from patients with osteogenesis imperfecta (OI) regarding different age groups and number of pamidronate treatment (PAM) cycles

OI children ^a		OI Type I (n = 58 DPRs)	OI Type III (n = 83 DPRs)	OI Type IV (n = 56 DPRs)
Age groups (years)	<5	2	10	3
	5–7	17	22	18
	8–10	14	27	11
	11–14	17	16	19
	15–19	8	9	5
Number of PAM cycles	0–4	33	23	21
	5–10	17	25	20
	>10	8	29	11
	Missing data ^b	0	6	4

DPR, dental panoramic radiograph.

^aAt the time of this study, OI classification was not defined for nine DPRs.^bThe missing data represent 12 DPRs of patients in which the number of PAM cycles could not be found.

and relative frequencies were calculated for the qualitative variables. Normal distribution of the data regarding FD measurements and the radiomorphometric indices were evaluated using Lilliefors test. Associations of FD measurements with both SVE and MCI were examined using *t* test for independent samples and one-way ANOVA, respectively. In cases of statistical significance, ANOVA test was followed by least significant difference–Fisher test. The correlations between the quantitative variables were tested with the Pearson correlation coefficient (*r*).

Factorial ANOVA and least significant difference–Fisher test were used to compare FD and MCW measurements in children with different types of OI for different PAM cycles (0–4, 5–10 or >10).

Finally, a linear regression model was performed using MCW and FD of the cortical bone. The significance of the model was verified by analysis of variance.

All statistical analysis was performed by Statistica v. 7.0 (StatSoft® Inc., Tulka, OK). *p*-values <0.05 indicated statistical significance.

Results

Table 1 demonstrates the characterization of DPRs in patients with OI regarding different age groups and number of PAM cycles. As no significant differences

were found between male and female, both sexes were evaluated altogether.

Relationship between qualitative DPR indices and OI

Regarding SVE, as the number of PAM cycles increases, there was a tendency to increase the number of children with cortex classified as not thin (**Table 2**).

As to MCI, children with OI Type III presented a higher frequency of C1 classification as the number of PAM cycles increases. Among children with other types of OI, the frequency of MCI classifications did not seem to be related to the number of PAM cycles (**Table 3**). There were corticals classified as C3 only at the first stage of PAM treatment (0–4 cycles) for all OI types.

An association was found between SVE and MCI ($\chi^2 = 10.47$, $p = 0.005$).

Relationship between SVE and quantitative measurements (MCW and FD)

An association was found between MCW and SVE ($p < 0.05$). Mean MCW values were lower in children with OI with inferior cortex classified as thin. In children with OI and cortex classified as not thin, MCW values ranged between 3.5 and 3.7 mm. For thin classification, MCW values ranged between 2.5 and 2.8 mm.

Regarding FD measurements, no association was found between SVE and the first and second ROIs ($p = 0.975$ and $p = 0.169$, respectively). On the other hand,

Table 2 Relationship between simple visual estimation of cortical width (SVE) and the number of intravenous pamidronate (PAM) cycles

OI type	Number of PAM cycles ^a	SVE classification	
		Thin, n (%)	Not thin, n (%)
OI Type I	0–4	19 (57.6%)	14 (42.4%)
	5–10	2 (11.2%)	15 (88.2%)
	>10	0	8 (100%)
OI Type III	0–4	8 (34.8%)	15 (65.2%)
	5–10	5 (20%)	20 (80%)
	>10	4 (13.8%)	25 (86.2%)
OI Type IV	0–4	9 (42.9%)	12 (57.1%)
	5–10	4 (20%)	16 (80%)
	>10	0	11 (100%)

OI, osteogenesis imperfecta.

^aThe numbers of PAM cycles were not registered in 10 cases (4 dental panoramic radiographs of patients with OI Type IV and 6 of OI Type III).

Table 3 Relationship between mandibular cortical index (MCI) and the number of intravenous pamidronate (PAM) cycles

OI type	Number of PAM cycles	MCI classification		
		C1, n (%)	C2, n (%)	C3, n (%)
OI Type I	0–4	28 (84.8%)	4 (12.1%)	1 (3%)
	5–10	13 (76.5%)	4 (23.5%)	0
	>10	7 (87.5%)	1 (12.5%)	0
OI Type III	0–4	9 (39.1%)	11 (47.8%)	3 (13%)
	5–10	19 (76%)	6 (24%)	0
	>10	22 (75.9%)	7 (24.1%)	0
OI Type IV ^a	0–4	17 (81%)	3 (14.3%)	1 (4.8%)
	5–10	18 (90%)	2 (10%)	0
	>10	7 (63.6%)	3 (27.3%)	1 (9.1%)

OI, osteogenesis imperfecta.

^aThe numbers of PAM cycles were not registered in 10 cases (4 dental panoramic radiographs of patients with OI Type IV and 6 of OI Type III).

the association of SVE was found for the FD of the cortical bone ($p < 0.001$). For not thin classification, FD measurements of the cortical bone ranged between 1.098 and 1.125. For thin classification, these FD measurements ranged between 1.020 and 1.057. Therefore, as the cortex was classified as thin, FD of the cortical bone presented lower values.

Relationship between MCI and quantitative measurements (MCW and FD)

An association was found between MCI and MCW measurements ($F_{2,204} = 6.945$; $p = 0.001$). Lower mean MCW values were found in children with C3 classification (Figure 3). In children with OI classified as C1 and C2, MCW values ranged between 3.2 and 3.6 mm. For C3 classification, MCW values ranged between 1.9 and 2.7 mm.

Significant differences were not found for FD measurements on the trabecular and cortical bones (ROI 1, $p = 0.645$; ROI 2, $p = 0.229$; ROI 3, $p = 0.466$).

Relationship between quantitative measurements (MCW and FD)

No correlation was found between MCW and FD measurements ($p > 0.05$), except for the correlation between MCW and FD of the cortical bone (ROI 3), with a significant correlation coefficient ($r = 0.616$, $p < 0.05$).

MCW and FD measurements regarding different types of OI and number of PAM cycles

Mean FD of trabecular bone measurements did not differ significantly among different types of OI and also among different number of PAM cycles ($p > 0.05$). On the other hand, there were significant differences between MCW and FD of the cortical bone, regarding

Figure 3 Relationship between mandibular cortical width and the mandibular cortical index. C1, the endosteal margin of the cortex was even and sharp; C2, the endosteal margin presented semi-lunar defects (lacunar resorption) or appeared to form endosteal cortical residues; or C3, the cortical layer formed heavy endosteal cortical residues and was clearly porous.

Figure 4 The mean mandibular cortical width (MCW) and fractal dimension (FD) of the cortical bone values are higher on dental panoramic radiographs of patients with osteogenesis imperfecta (OI) after pamidronate treatment. (a) Comparison of mean values and confidence intervals of MCW measurements between children with different types of osteogenesis in relation to the number of pamidronate cycles. (b) Comparison of mean values and confidence intervals of FD measurements [region of interest 3 (ROI 3)] between children with different types of osteogenesis in relation to the number of pamidronate cycles. (c) Scatter plot between mandibular cortical width and FD measurements of the cortical bone (ROI 3).

different types of OI and number of PAM cycles ($F_{4,178} = 0.201, p = 0.037$ and $F_{4,178} = 2.173, p = 0.044$, respectively). The mean values and confidence intervals of MCW and FD of the cortical bone in relation to different OI types and number of PAM cycles are presented in Figure 4a and Figure 4b, respectively. Figure 4c shows the scatter plot between MCW and FD measurements of the cortical bone (ROI 3).

Discussion

To our knowledge, the current study was the first to evaluate several dental panoramic indices and FD measurements in children with OI. Although there were several studies addressing the correlation between DPRs and BMD in adults,^{12–29} proposing that it is a viable screening tool for low bone mass identification, a research in a population of children with low BMD would be required. A previous study demonstrated that MCW was affected by PAM treatment.³⁵ In the present study, DPRs of OI children presented erosion and thinning of the inferior mandibular cortical bone. The results indicated that the thickness of the inferior mandibular cortex and FD of the same cortical bone seem to be the most promising measurements. Regarding different types of OI and number of PAM cycles, the differences were significant only for the FDs of the cortical bone and MCW. Nevertheless, there were correlations between the qualitative and quantitative DPR indices, except for the FD of the trabecular bone.

FD measurements of the trabecular bone were not statistically different among OI types nor PAM cycles; also, they did not present association with the qualitative indices and had weak correlation with cortical bone measurements. Although FD has been proven to be efficient in evaluating bone quality on several bone sites, several studies^{20–28} have shown controversial results when analyzing FD on DPRs of patients with osteoporosis. The negative results for the trabecular bone may be then related to two factors: the possibility that the trabecular bone does not reflect jaw microarchitecture as it does in other bones; the second point to be considered is the fact that the principal effect of PAM treatment is on cortical bone width, with little effect on trabecular bone thickness.

A previous study has found higher FD values at alveolar regions of the mandible than controls in patients with bisphosphonate-associated osteonecrosis of the jaws.³⁶ The authors suggested that FD could be a promising tool for detecting bone alterations in adult patients taking bisphosphonates. FD analysis in the aforementioned study has been performed on CBCT, which precludes a direct comparison with the results of the present study. Furthermore, FD can only be reliably compared when using radiographs at the same spatial resolution.²⁶

In our present study, only FD analysis of the cortical bone showed statistical difference among OI types and PAM cycle classes, although the statistical significance

seems to be lower than in MCW. Regarding MCW, this was the variable that best showed the differences among OI type and PAM cycles. Regarding this variable, at the beginning of treatment (0–4 cycles), all OI types had lower and equivalent values, mean of 2.9 mm, which corresponds to its extreme bone fragility and reason to begin PAM treatment. At the class from 5–10 cycles, the less severe types, I and IV, had shown a statistic increase in cortical thickness, mean of 3.5 mm, whereas Type III had a significant increase only with >10 cycles. Still, at this last class of cycles, OI Types I and IV showed a continuous growth of its MCW, with means much higher than the cut-off point for low bone mass in adults (mean of 4.3 mm). The continuous increase of the inferior mandibular cortex through PAM treatment leads us to believe that mandibular bone response to PAM infusions is different from other bones. A previous adult study with CBCT stated that mandibular cortical measurement is a potentially useful tool in the detection of bone dimensional changes caused by bisphosphonates.³⁷

The mechanism of action of bisphosphonates in children is different from adults, as bone in children is a growing tissue and responds to the drug differently than the adult bone. Therefore, such difference precludes the generalizability of our results regarding the PAM effect on the cortical bone in children and adults. Childhood and adolescence are the most important periods in terms of bone mass acquisition and spinal growth, since the bone that must last a lifetime is made between the ages of 10 and 18 years.³²

Regarding qualitative indices, SVE showed an increase in the number of the mandibular cortices classified as not thin over PAM cycles, which corroborates previous publications about other bones of the body, which state that the thickness of the cortical nearly doubles in the first years of administration of bisphosphonates.^{6,7} On the other hand, the relationship between MCI and PAM treatment was not so clear, except by the fact that C3 cortices—the most porous ones and associated with osteoporosis cases—were found only in the initial phase of treatment (0–4 cycles) when bones are still very fragile for all types of OI.

These two indices showed a positive association with each other, thus, children with more mandibular cortices (C3) tended to present them visually thinner. Other relevant information is that these indices were associated with MCW, allowing to assign numerical values to define the qualitative categories. The mean thickness of this category coincided with the cut-off number for low BMD in adults, 3 mm, suggested in previous publications.^{17,38,39} This finding suggests that a simple visual assessment, without the need for sophisticated tools or softwares, can provide an idea of the evolution of PAM treatment in children with OI, by comparing serial panoramic radiographs.

This longitudinal study was retrospective and, as such, limited. The selected children for the study were not subjected to bone densitometry examinations. In addition, the radiographic procedures were carried out at different times and ages among the children, as the panoramic examinations were conditioned to the date of hospitalization of the children. On the other hand, the current study is the first one to evaluate radiomorphometric indices and FD in children with OI and to verify mandibular cortical changes through PAM treatment. Further researches are necessary, using a larger sample, to evaluate the correlation between this cortical measurements and BMD in children, and also to access whether a DPR can preview treatment outcomes with bisphosphonates.

In conclusion, our results verified that children with OI presented cortical bone alterations after starting PAM treatment, and that both MCW and the FD of the cortical bone were higher in children with OI after PAM treatment. Therefore, these findings provide preliminary evidence that only cortical bone should be considered for analyzing patients with OI, as well as to monitor the progress of treatment with PAM. The thinning of the mandibular cortex depends on the number of PAM cycles and the OI type. Prospective studies are necessary to verify whether DPRs may be considered as an auxiliary tool for other conditions related to low BMD, and also for previewing treatment outcomes in such populations.

References

- Ben Amor M, Rauch F, Monti E, Antoniazzi F. Osteogenesis imperfecta. *Pediatr Endocrinol Rev* 2013; **10**(Suppl. 2): 397–405.
- Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. *J Med Genet* 1979; **16**: 101–16. doi: <http://dx.doi.org/10.1136/jmg.16.2.101>
- Van Dijk FS, Sillence DO. Osteogenesis imperfecta: clinical diagnosis, nomenclature and severity assessment. *Am J Med Genet A* 2014; **164A**: 1470–81. doi: <http://dx.doi.org/10.1002/ajmg.a.36545>
- Byers PH, Pyott SM. Recessively inherited forms of osteogenesis imperfecta. *Annu Rev Genet* 2012; **46**: 475–97. doi: <http://dx.doi.org/10.1146/annurev-genet-110711-155608>
- Cheung MS, Glorieux FH. Osteogenesis imperfecta: update on presentation and management. *Rev Endocr Metab Disord* 2008; **9**: 153–60. doi: <http://dx.doi.org/10.1007/s11154-008-9074-4>
- Marini JC, Blissett AR. New genes in bone development: what's new in osteogenesis imperfecta. *J Clin Endocrinol Metab* 2013; **98**: 3095–103. doi: <http://dx.doi.org/10.1210/jc.2013-1505>
- Rauch F, Glorieux FH. Osteogenesis imperfecta. *Lancet* 2004; **363**: 1377–85. doi: [http://dx.doi.org/10.1016/S0140-6736\(04\)16051-0](http://dx.doi.org/10.1016/S0140-6736(04)16051-0)
- Glorieux FH. Treatment of osteogenesis imperfecta: who, why, what? *Horm Res* 2007; **68**(Suppl. 5): 8–11. doi: <http://dx.doi.org/10.1159/000110463>
- Harrington J, Sochett E, Howard A. Update on the evaluation and treatment of osteogenesis imperfecta. *Pediatr Clin North Am* 2014; **61**: 1243–57. doi: <http://dx.doi.org/10.1016/j.pcl.2014.08.010>
- Zeitlin L, Rauch F, Plotkin H, Glorieux FH. Height and weight development during four years of therapy with cyclical intravenous pamidronate in children and adolescents with osteogenesis imperfecta types I, III, and IV. *Pediatrics* 2003; **111**: 1030–6. doi: <http://dx.doi.org/10.1542/peds.111.5.1030>

11. Rauch F, Travers R, Plotkin H, Glorieux FH. The effects of intravenous pamidronate on the bone tissue of children and adolescents with osteogenesis imperfecta. *J Clin Invest* 2002; **110**: 1293–9. doi: <http://dx.doi.org/10.1172/JCI15952>
12. Klemetti E, Kolmakov S, Heiskanen P, Vainio P, Lassila V. Panoramic mandibular index and bone mineral densities in postmenopausal women. *Oral Surg Oral Med Oral Pathol* 1993; **75**: 774–9. doi: [http://dx.doi.org/10.1016/0030-4220\(93\)90438-A](http://dx.doi.org/10.1016/0030-4220(93)90438-A)
13. Taguchi A, Suei Y, Ohtsuka M, Otani K, Tanimoto K, Ohtaki M. Usefulness of panoramic radiography in the diagnosis of postmenopausal osteoporosis in women. Width and morphology of inferior cortex of the mandible. *Dentomaxillofac Radiol* 1996; **25**: 263–7. doi: <http://dx.doi.org/10.1038/dmfr.25.5.9161180>
14. Alonso MB, Cortes AR, Camargo AJ, Arita ES, Haiter-Neto F, Watanabe PC. Assessment of panoramic radiomorphometric indices of the mandible in a Brazilian population. *ISRN Rheumatol* 2011; 2011: 854287. doi: <http://dx.doi.org/10.5402/2011/854287>
15. Devlin H, Allen P, Graham J, Jacobs R, Nicopoulou-Karayianni K, Lindh C, et al. The role of the dental surgeon in detecting osteoporosis: the OSTEODENT study. *Br Dent J* 2008; **204**: E16. doi: <http://dx.doi.org/10.1038/sj.bdj.2008.317>
16. Lee K, Taguchi A, Ishii K, Suei Y, Fujita M, Nakamoto T, et al. Visual assessment of the mandibular cortex on panoramic radiographs to identify postmenopausal women with low bone mineral densities. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005; **100**: 226–31. doi: <http://dx.doi.org/10.1016/j.tripleo.2004.11.052>
17. Ferreira Leite A, de Souza Figueiredo PT, Ramos Barra F, Santos de Melo N, de Paula AP. Relationships between mandibular cortical indexes, bone mineral density, and osteoporotic fractures in Brazilian men over 60 years old. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2011; **112**: 648–56. doi: <http://dx.doi.org/10.1016/j.tripleo.2011.06.014>
18. Vlasidis KZ, Damilakis J, Velegakis GA, Skouteris CA, Fragouli I, Goumenou A, et al. Relationship between BMD, dental panoramic radiographic findings and biochemical markers of bone turnover in diagnosis of osteoporosis. *Maturitas* 2008; **59**: 226–33. doi: <http://dx.doi.org/10.1016/j.maturitas.2008.01.006>
19. Roberts M, Yuan J, Graham J, Jacobs R, Devlin H. Changes in mandibular cortical width measurements with age in men and women. *Osteoporos Int* 2011; **22**: 1915–25. doi: <http://dx.doi.org/10.1007/s00198-010-1410-3>
20. Sindeaux R, Figueiredo PT, de Melo NS, Guimarães AT, Lazarte L, Pereira FB, et al. Fractal dimension and mandibular cortical width in normal and osteoporotic men and women. *Maturitas* 2014; **77**: 142–8. doi: <http://dx.doi.org/10.1016/j.maturitas.2013.10.011>
21. Yaşar F, Akgünlü F. The differences in panoramic mandibular indices and fractal dimension between patients with and without spinal osteoporosis. *Dentomaxillofac Radiol* 2006; **35**: 1–9.
22. Yaşar F, Akgunlu F. Evaluating mandibular cortical index quantitatively. *Eur J Dent* 2008; **2**: 283–90.
23. Geraets WG, Van der Stelt PF, Netelenbos CJ, Elders PJ. A new method for automatic recognition of the radiographic trabecular pattern. *J Bone Miner Res* 1990; **5**: 227–33. doi: <http://dx.doi.org/10.1002/jbmr.5650050305>
24. Geraets WG, Van der Stelt PF, Elders PJ. The radiographic trabecular bone pattern during menopause. *Bone* 1993; **14**: 859–64. doi: [http://dx.doi.org/10.1016/8756-3282\(93\)90315-2](http://dx.doi.org/10.1016/8756-3282(93)90315-2)
25. White SC, Rudolph DJ. Alterations of the trabecular pattern of the jaws in patients with osteoporosis. *Oral Surg Oral Med Oral Pathol* 1999; **88**: 628–35. doi: [http://dx.doi.org/10.1016/S1079-2104\(99\)70097-1](http://dx.doi.org/10.1016/S1079-2104(99)70097-1)
26. 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. doi: <http://dx.doi.org/10.1007/s00784-012-0882-2>
27. Tosoni GM, Lurie AG, Cowan AE, Burleson JA. Pixel intensity and fractal analyses: detecting osteoporosis in perimenopausal and postmenopausal women by using digital panoramic images. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **102**: 235–41. doi: <http://dx.doi.org/10.1016/j.tripleo.2005.08.020>
28. Alman AC, Johnson LR, Calverley DC, Grunwald GK, Lezotte DC, Hokanson JE. Diagnostic capabilities of fractal dimension and mandibular cortical width to identify men and women with decreased bone mineral density. *Osteoporos Int* 2012; **23**: 1631–6. doi: <http://dx.doi.org/10.1007/s00198-011-1678-y>
29. Kavitha MS, An SY, An CH, Huh KH, Yi WJ, Heo M, et al. Texture analysis of mandibular cortical bone on digital dental panoramic radiographs for the diagnosis of osteoporosis in Korean women. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015; **119**: 346–56. doi: <http://dx.doi.org/10.1016/j.oooo.2014.11.009>
30. Eckstein F, Matsuura M, Kuhn V, Priemel M, Müller R, Link TM, et al. Sex differences of human trabecular bone microstructure in aging are site-dependent. *J Bone Miner Res* 2007; **22**: 817–24. doi: <http://dx.doi.org/10.1359/jbmr.070301>
31. Bachrach LK. Consensus and controversy regarding osteoporosis in the pediatric population. *Endocr Pract* 2007; **13**: 513–20. doi: <http://dx.doi.org/10.4158/EP.13.5.513>
32. Hough JP, Boyd RN, Keating JL. Systematic review of interventions for low bone mineral density in children with cerebral palsy. *Pediatrics* 2010; **125**: e670–8. doi: <http://dx.doi.org/10.1542/peds.2009-0292>
33. Gatti D, Colapietro F, Fracassi E, Sartori E, Antoniazzi F, Braga V, et al. The volumetric bone density and cortical thickness in adult patients affected by osteogenesis imperfecta. *J Clin Densitom* 2003; **6**: 173–7. doi: <http://dx.doi.org/10.1385/JCD:6:2:173>
34. Rauch F, Land C, Cornibert S, Schoenau E, Glorieux FH. High and low density in the same bone: a study on children and adolescents with mild osteogenesis imperfecta. *Bone* 2005; **37**: 634–41. doi: <http://dx.doi.org/10.1016/j.bone.2005.06.007>
35. Apolinário AC, Figueiredo PT, Guimarães AT, Acevedo AC, Castro LC, Paula AP, et al. Pamidronate affects the mandibular cortex of children with osteogenesis imperfecta. *J Dent Res* 2015; **94**(Suppl. 3): 95S–102S. doi: <http://dx.doi.org/10.1177/0022034514567334>
36. Torres SR, Chen CS, Leroux BG, Lee PP, Hollender LG, Schubert MM. Fractal dimension evaluation of cone beam computed tomography in patients with bisphosphonate-associated osteonecrosis. *Dentomaxillofac Radiol* 2011; **40**: 501–5. doi: <http://dx.doi.org/10.1259/dmfr/14636637>
37. Torres SR, Chen CS, Leroux BG, Lee PP, Hollender LG, Santos EC, et al. Mandibular cortical bone evaluation on cone beam computed tomography images of patients with bisphosphonate-related osteonecrosis of the jaw. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2012; **113**: 695–703. doi: <http://dx.doi.org/10.1016/j.oooo.2011.11.011>
38. Devlin H, Horner K. Mandibular radiomorphometric indices in the diagnosis of reduced skeletal bone mineral density. *Osteoporos Int* 2002; **13**: 373–8. doi: <http://dx.doi.org/10.1007/s001980200042>
39. Taguchi A, Sugino N, Miki M, Kozai Y, Mochizuki N, Osanai H, et al. Detecting young Japanese adults with undetected low skeletal bone density using panoramic radiographs. *Dentomaxillofac Radiol* 2011; **40**: 154–9. doi: <http://dx.doi.org/10.1259/dmfr/30045588>