CLINICAL INVESTIGATIONS

Pamidronate Affects the Mandibular Cortex of Children with Osteogenesis Imperfecta

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Abstract: We hypothesized that mandibular cortical width (MCW) is smaller in children with osteogenesis imperfecta (OI) than in healthy children and that pamidronate can improve the cortical mandibular thickness. The aim of this study was to assess changes in the MCW on dental panoramic radiographs (DPRs) of children with normal bone mineral density (BMD) and with OI. We also compared the MCW of children with different types of OI regarding the number of pamidronate cycles and age at the beginning of treatment. MCW measurements were retrospectively obtained from 197 DPRs of 66 children with OI types I, III, and IV who were in treatment with a comparable dosage of cyclical intravenous pamidronate between 2007 and 2013. The control group had 92 DPRs from normal BMD children. Factorial analysis of variance was used to compare MCW measurements among different age groups and between sexes and also to compare MCW measurements of children with different types of OI among different pamidronate cycles and age at the beginning of treatment. No significant differences in results were found between male and female sub-

jects in both OI and healthy children, so they were evaluated altogether ($P > 0.05$). There was an increase of MCW values related to aging in all normal BMD and OI children but on a smaller scale in children with OI types I and III. Children with OI presented lower mean MCW values than did children with normal BMD at the beginning of treatment ($P < 0.05$). A linear model estimated the number of pamidronate cycles necessary to achieve mean MCW values equivalent to those of healthy children. The thinning of the mandibular cortex depended on the number of pamidronate cycles, the type of OI, and the age at the beginning of treatment. DPRs could thus provide a way to identify cyclic pamidronate treatment outcomes in patients with OI.

Key Words: panoramic radiography, bone density, diphosphonate, bone diseases, mandible, child.

Introduction

Osteogenesis imperfecta (OI) is a connective tissue disorder characterized by low bone mass and increased susceptibility to fractures. Severity varies, ranging from intrauterine lethality to mild

forms without fractures. The original classification distinguishes 4 major types, with severity increasing as follows: I < IV < III < II (Sillence et al. 1979). Diagnosis is based on clinical and radiographic findings and mode of inheritance. Since then, other classifications have been proposed (Cheung and Glorieux 2008; Byers and Pyott 2012).

Multidisciplinary OI treatment aims to prevent bone deformities and maximize functional capabilities (Glorieux 2007). Intravenous pamidronate treatment (PAM), which inhibits the function of osteoclasts, has shown to increase bone mineral density (BMD), reduce bone pain, decrease fracture rate, and improve growth, muscle strength, and mobility in patients since birth (Zeitlin et al. 2003; Kusumi et al. 2014). Histomorphometric studies of iliac bone samples showed an increase of cortical width as its main effect and also an increased number of bone trabeculae. Growth of the cortical width is higher in the first 2 to 3 y of treatment, but the changes lessen after this period (Rauch et al. 2006). Despite the benefits, bisphosphonate intake for a long period may cause reduction in bone turnover, which can lead to a delay in fracture repair (Melo and Obeid 2005; Nicolaou et al. 2012). Nevertheless,

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side effects of long-term PAM treatment should be further investigated.

Children with OI have low BMD (Alvarez et al. 2003). Although BMD seems to be an indicator of OI severity, the available densitometric evidence is limited for patients with OI because of difficulties in results interpretation due to the small size of these patients' bones, deformities, vertebral compression fractures, scoliosis, and history of prolonged immobilization. Despite difficulties, BMD increases during PAM treatment (Dwan et al. 2014).

Dental panoramic radiograph (DPR) indices have been used to verify the appearance of the mandibular cortex compared with BMD assessment. Mandibles of osteoporotic subjects have reduced bone mass and altered morphology, which may be observed through the thinning and resorption of the inferior border of the mandibular cortical bone (Devlin and Horner 2002; Taguchi et al. 2006; Leite et al. 2010; Nagi et al. 2014). The most used index measures the mandibular cortical width (MCW) below the mental foramen. This index has also been used in pediatric patients (Paulsson-Björnsson et al. 2014). However, to our knowledge, data regarding the relationship between MCW and children with low bone mass are still not available.

The purpose of the present study was to assess changes in MCW on DPRs of children with normal BMD and with OI. We also compared MCW on DPRs of children with different types of OI regarding the number of pamidronate cycles and age at the beginning of treatment. The hypothesis was that MCW is smaller in children with OI than in healthy children and that pamidronate can improve the cortical mandibular thickness.

Materials and Methods

The patient sample was selected from an existing database of 105 patients with OI from the University Hospital of Brasília. All patients had been evaluated by the Pediatric Endocrinology Center and were under follow-up at the Oral

Care Center at our institution. To be included in the study, DPRs of children had to be performed according to technical quality criteria, and the mandible cortex needed to be completely visible. Patients 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 were being treated with cyclic PAM between 2007 and 2013. The sample size had sufficient statistical power with distribution *t* and *F* equivalent to 0.99 (effect size = 0.3 and type I errors = 0.05). Pamidronate was administered at 4-mo intervals on 2 or 3 consecutive days, to children older than 3 y, at a dosage of 1.0 mg/kg/d for the 3-d cycle; for the 2-d scheme, the dosage was 1.5 mg/kg/d, and the annual cumulative dosage was 9 mg/kg. The radiographs were taken at different times during PAM treatment. DPRs were performed at the time of admission for the PAM cycle. Therefore, the number of DPRs corresponds to the number of hospitalizations of each patient. The research was carried out through the comparison of X-ray measurements performed at different times during the treatment. Medical and dental data regarding long-term complications of the PAM therapy were recorded, including osteonecrosis of the jaw.

The control group consisted of 92 age- and sex-matched healthy children under dental treatment who required DPRs. All patients underwent dual-energy X-ray absorptiometry (DXA) of the lumbar spine (L1 to L4) and total body by using a Lunar DPX-NT (General Electric, Fairfield, CT, USA). BMD values were classified as normal (*z* score >-2.0) or low bone mass (*z* score ≤ -2.0 in at least one of the sites). By using wrist X-rays, baseline DXA reports in children were adjusted for growth and maturation, based on bone age results (International Society for Clinical Densitometry 2013).

The DPRs and DXA of the control group were performed on the same day by using the same techniques and devices for the OI group. The DXA examiner was blinded to the DPR results.

This study was approved by the Research Ethics Committee of the University of Brasília, Brazil, and informed consent was obtained from all individuals.

MCW Measurements in DPRs of Children with Normal BMD and OI

DPRs were performed for all individuals by using the same panoramic machine (Rotograph Plus; Villa Medical System, Buccinasco, Italy). All radiographs were scanned (Epson Exp, 1680Pro; Seiko Epson Corp, Nagano, Japan), with 8-bit gray scale and 300 dpi resolution. The images were saved in JPEG format, with 3188×1709 pixels and 256 gray levels. The images were analyzed once by an experienced professional using ImageJ software, available at <http://rsb.info.nih.gov/nih-image>. MCW was measured on the side of better visualization, below the mental foramen, as described in previous studies with adults and children (Taguchi et al. 1995; Nagi et al. 2014; Paulsson-Björnsson et al. 2014). The observer was blinded to both OI and healthy diagnoses. Parallel to the long axis of the mandible and tangential to the inferior border, a line was drawn on the image using the ImageJ software tools. Perpendicular to this tangent intersecting the inferior border of the mental foramen, a line was constructed, along which the upper and lower delimitation points of the inferior mandibular cortex were located. Then, MCW was measured (Fig. 1).

Statistical Analyses

After checking normal distribution data of MCW and homoscedasticity (Lilliefors test and Bartlett test), parametric analyses were performed. MCW measurements were compared across different age groups and between sexes by using factorial analysis of variance (ANOVA). Factorial ANOVA and least significant difference (LSD)-Fisher tests were used to compare MCW in children with different types of OI for different pamidronate

cycles (0 to 4, 5 to 10, or >10) and age at the beginning of treatment (0 to 5 or >5 y). DXA data were correlated with MCW in 98 healthy children by using simple linear regression, and the parameters were analyzed with ANOVA type III. Finally, a predictive model on the necessary number of pamidronate cycles was constructed with multiple regression, applying the stepwise method and Akaike criteria. A *P* value less than 0.05 was considered statistically significant. The model significance was also evaluated by ANOVA type III. All statistical analyses were performed by Statistica 7.0 software (StatSoft, Tulsa, OK, USA).

Results

As no significant differences in results were found between male and female participants, both sexes were evaluated together ($F_{3,248} = 0.780$; $P = 0.505$).

Table 1 shows the number of DPRs taken from patients with OI regarding different age groups, number of PAM cycles, and age at the beginning of treatment.

Regarding MCW measurements of children with normal BMD, the values were significantly different throughout the age groups ($P < 0.05$), presenting mean equivalence only from ages 8 to 10 y and 11 to 14 y ($P > 0.05$). Table 2 shows the comparison of MCW in healthy children and those with OI in the different age groups. Among children with OI, MCW was different across age groups, presenting mean equivalence from ages 5 to 7 y and 8 to 10 y, as well as from ages 11 to 14 y and 15 to 19 y. When comparing children with normal BMD and those with OI, MCW was statistically different across the age groups, except for children between ages 11 and 14 y. Figure 2A shows the increase of MCW with aging in all children with normal BMD and OI but on a smaller scale in OI types I and III.

Figure 2B shows the comparison of MCWs among all OI types and children with normal BMD. From such analyses, we found the following about OI children in comparison with healthy children ($F_{6,421} = 7.408$; $P = 0.001$):

Figure 1.

Mandibular cortical width measurement (MCW). (A) Graphic representation of MCW measurement. (B) MCW measurement on a dental panoramic radiograph of a child with osteogenesis imperfecta.

- All types of OI with 0 to 4 PAM cycles showed lower MCWs.
- OI types I and IV with 5 to 10 PAM cycles showed equivalent mean values of MCW.
- OI type III showed equivalent MCW after 10 cycles.
- OI types I and IV with more than 10 cycles presented higher MCWs.

Taking into consideration the PAM effects on MCW, Figure 2C shows the changes in MCW of children with OI who had begun treatment at an early age (0 to 5 y) and after the age of 5 y. They both followed the same tendency, but it was more accelerated in the group beginning treatment after 5 y.

Children with OI types I and IV who had begun treatment between ages 0 and 5 y presented an increase in MCW mean only after 10 PAM cycles, but those who had begun treatment after 5 y had an

increase with 5 to 10 PAM cycles ($P < 0.05$). Children with OI type III presented a significant increase only after 10 PAM cycles, despite their age at the beginning of treatment. The mean MCWs were equivalent for children who had received 0 to 4 PAM cycles, as well as 5 to 10 cycles, regardless of OI type and age at the beginning of treatment. In children who had begun treatment earlier and with more than 10 PAM cycles, the mean MCWs were lower in OI type III than in types I and IV. Children who had begun treatment after 5 y and received more than 10 PAM cycles had similar MCW in all OI types.

There were no long-term complications detected after PAM cycles.

Correlation between MCW and DXA in Children with Normal BMD

Linear regression models for MCW and DXA values of lumbar spine and total

Table 1.

Number of Panoramic Radiographs Taken from Patients with Osteogenesis Imperfecta Regarding Different Age Groups, Number of Pamidronate Cycles, and Age at the Beginning of Treatment

Characteristic		OI Type I (n = 58 DPRs)	OI Type III (n = 83 DPRs)	OI Type IV (n = 56 DPRs)
Age groups, y	<5	2	10	3
	5 to 7	17	22	18
	8 to 10	14	27	11
	11 to 14	17	15	19
	15 to 19	8	9	5
Number of intravenous pamidronate cycles	0 to 4	33	23	21
	5 to 9	17	21	19
	>10	8	33	12
	Missing data	0	6	4
Age at the beginning of treatment, y	0 to 5	21	44	16
	>5	37	39	36
	Missing data	0	0	4

DPRs, dental panoramic radiographs; OI, osteogenesis imperfecta.

Table 2.

Comparison of Mandibular Cortical Width Measurements in Healthy Children and in Children with Osteogenesis Imperfecta across Different Age Groups

Children	Age Groups, y	Number of DPRs	Mean, mm ^a	SD, mm	95% CI, mm
Normal BMD	5 to 7	32	3.38 ^{aA}	0.62	3.15, 3.60
	8 to 10	26	3.81 ^{bA}	0.68	3.54, 4.09
	11 to 14	18	3.79 ^{bA}	0.54	3.52, 4.06
	15 to 19	6	4.45 ^{cA}	0.43	4.00, 4.90
OI	5 to 7	57	3.04 ^{aB}	0.63	2.87, 3.21
	8 to 10	52	3.20 ^{aB}	0.67	3.02, 3.39
	11 to 14	51	3.83 ^{bA}	0.80	3.60, 4.05
	15 to 19	22	3.78 ^{bB}	0.80	3.43, 4.13

BMD, bone mineral density; CI, confidence interval; DPRs, dental panoramic radiographs; OI, osteogenesis imperfecta; SD, standard error.

^aWithin-group comparisons: means followed by the same lowercase letter are not significantly different for children with normal bone mineral density or those with OI. Between-group comparisons: means followed by the same capital letter are not significantly different between for children with normal bone mineral density or those with OI.

body were constructed. In both cases, a significant correlation between the variables was found ($r = 0.64$, $P < 0.05$; $r = 0.63$, $P < 0.05$, respectively).

Predictive Model for Necessary PAM Cycles and Relative Variables for OI Treatment

A general linear model to predict how many PAM cycles were needed to achieve mean MCW values equivalent to healthy

children was constructed. Correlation parameters of ages, MCW, and OI types were established. Also, the final number of PAM cycles (fPAM) was considered the dependent variable (Y), and the independent variables (X) were OI type, age at the first X-ray (iA), age at the last X-ray (fA), initial number of PAM cycles (iPAM), initial MCW value (iMCW), and final MCW value (fMCW). In the final adjustment, the number of necessary PAM

cycles (fPAM) was related to the number of initial PAM cycles, as well as initial and final MCW values, as seen in Figure 3.

Discussion

As far as we know, this is the first research to evaluate MCW in patients with OI. Previous studies have verified differences related to BMD in the elderly population by MCW (Devlin and

Horner 2002; Leite et al. 2010; Alonso et al. 2011; Nagi et al. 2014). While other studies have verified that PAM treatment increases BMD in children with OI, our study was intended to analyze mandibular cortical bone changes throughout it, as demonstrated in other bone sites (Zeitlin et al. 2003; Rauch et al. 2006). DPRs are widely used as a complement to diagnoses, but they may also provide information about bisphosphonate intake and bone alterations. Such radiographs of the MCW may allow dentists to refer patients with OI to medical professionals for further examinations.

Mean MCW values presented no significant difference between the sexes, different from other studies that have found differences between both sexes in the elderly, possibly related to the aging characteristic of the samples. Therefore, all analyses were performed without sex distinction, following the tendency of other studies that evaluated PAM effect in patients with OI (Miller and Hangartner 1999; Crabtree et al. 2004).

Significant differences in MCW were found between healthy children and those with OI in all age classes, except the 11 to 14 y group. This discrepant result may be related to the fact that 72.72% of the subjects in this group had received already more than 5 PAM cycles, of whom almost half (33%) had received more than 10 PAM cycles, while in other age classes, the percentages of children with more than 5 cycles were 42%, 59%, and 68% for ages 5 to 7, 8 to 10, and 15 to 19 y, respectively. Besides, only children with OI type III had lower mean MCW than did healthy ones as they reached more than 10 PAM cycles, and in the 11 to 14 y age group, two-thirds of the subjects were OI types I and IV, which may have introduced a bias, increasing mean MCW for this age class.

In adult studies, the correlations between age, MCW, and BMD have been shown (Devlin and Horner 2002; Dutra et al. 2005; Leite et al. 2010). MCW was first studied in children at the mandibular angle, where, because of mandibular growth, the cortex is thinner, especially

Figure 2.

Mean mandibular cortical width (MCW) values are lower on dental panoramic radiographs of patients with osteogenesis imperfecta compared with children with normal bone mineral density. **(A)** Comparison of mean values and confidence intervals of MCW measurements between healthy children and those with osteogenesis imperfecta in different age groups. **(B)** Comparison of mean values and confidence intervals of MCW measurements between healthy and all kinds of osteogenesis imperfecta types in children with different pamidronate cycles. **(C)** Comparison between mean and confidence intervals of MCW measurements among the types of osteogenesis imperfecta in different cycles of intravenous pamidronate treatment that commenced before and after the age 5 y. OI, osteogenesis imperfecta.

Figure 3.

Surface graph representative of predictive model for necessary pamidronate treatment (PAM) cycles and relative variables for osteogenesis imperfecta treatment. *delta MCW = fMCW – iMCW. MCW, mandibular cortical width; fPAM, final number of pamidronate cycles; iPAM, initial number of pamidronate cycles; iMCW, initial mandibular cortical width value; fMCW, final MCW value.

Equation of the model:

$$fPAM = 10.31 + 0.91 * iPAM - 5.43.iMCW + 3.86*fMCW$$

in younger children (Bras et al. 1982). Taguchi et al. (2011) found a relationship between MCW and heel bone mass measured by calcaneus quantitative ultrasonography in individuals aged 18 to 36 y.

Our study has shown positive correlations between MCW and BMD in healthy children. Mean MCW values were higher than 3.0 mm, and lower values were found only in children ages 5 to 8 y. The lack of earlier studies in children precludes direct comparisons with our results. On the other hand, our data are consistent with adult studies, which indicate a cutoff of 3.0 mm for the correlation with low BMD (Taguchi et al. 2006; Leite et al. 2010).

Regarding children with OI, MCW increased with aging in all types but on a larger scale and with greater variability for type IV. The difficulty of defining OI type IV may explain our results since

its diagnosis is not well established, as it tends to encompass the phenotypes among OI types I and III (Arundel and Bishop 2010).

Our study has demonstrated that, independently from age at the beginning of treatment, MCW values followed the same growth tendency among different OI types. Mean MCW in children with OI type III and those with OI types I and IV who had begun treatment earlier presented a statistical difference only after 10 PAM cycles, while in children with OI types I and IV who had begun treatment after 5 y, the difference appeared at 5 to 10 cycles. The benefits of PAM treatment are highly perceived in the more severe phenotypes by reducing the number of fractures and deformities. However, as bone quality is worse in OI type III, the effect on the cortical bone width is still smaller than in the other types.

Children with OI types I and IV who had more than 10 PAM cycles presented higher MCW than did healthy children, showing a possible continuous effect of long-term PAM on mandibular cortical growth. The number of PAM cycles affects MCW differently than other bone sites (Rauch et al. 2006). Mandibular cells are more susceptible to a PAM effect, causing a less organized bone regeneration and homeostasis deregulation (Stefanik et al. 2008). Bisphosphonates have a positive effect on cortical bone by allowing customary periosteal growth while reducing the rate of endocortical bone remodeling and slowing bone loss from the endocortical surface (Torres et al. 2012).

Our study estimated the number of PAM cycles in children with OI necessary to achieve mean MCW values compatible to healthy children of a specific age. A linear model was used for this purpose, considering 1) the increase in BMD followed by PAM treatment (Dwan et al. 2014), 2) the relationship between MCW and BMD found in the healthy children in our study, and 3) the increase in MCW throughout PAM cycles. Thus, it seems possible to predict the amount of final PAM cycles from initial and final MCW values, estimated for the child's age. This linear model may be an important tool to preview the outcome of PAM and should be further tested in other populations.

The long-term consequences of PAM during growth are little known and should be further investigated (Rauch et al. 2007). In agreement with Kusumi et al. (2014), we believe that the benefits of decreased fracture rate in children receiving PAM justify the risks. In our study, no long-term side effects of PAM therapy, including osteonecrosis of the jaws, were found.

MCW measurement on DPRs may be accurate for identifying patients with low BMD (Dutra et al. 2007; Deguchi et al. 2008). The inferior cortex of the mandible is clearly visible and, therefore, is one of the most suitable structures for the aforementioned purpose. Furthermore, the distance of the mental foramen from the inferior border of the mandible remains relatively constant throughout

adult life (Klemetti et al. 1994). However, limitations of the DPR technique are its 2-dimensional representation, intrinsic distortional effects, and observer variability. Intrinsic errors are highly dependent on several factors, such as machine motion, mandible morphology, region studied, and patient positioning (Nikneshan et al. 2013; Riecke et al. 2014). Vertical measurements should preferably be made in areas anatomically oriented in the plane as the center of the image layer (Dutra et al. 2007). Fortunately, MCW is measured approximately in this plane, and so long as careful attention is given to positioning during radiography, it is likely that the distortional effects would have little influence on the cortical measurement (Devlin and Horner 2002). In addition, to avoid observer variability, a systematic approach is recommended for the interpretation of this image type (Perschbacher 2012).

This longitudinal study was retrospective and as such was limited. We did not have densitometric data of children with OI available, which would be important to verify the relationship between BMD and MCW in children with OI. In addition, the times of performing the radiographic procedures were different as well as the age at the beginning of treatment. Our study is the first to evaluate MCW in children with OI and to verify mandibular cortical changes in healthy children and those with OI. Further research is necessary to evaluate the correlation between MCW and BMD in children and also whether DPRs can preview treatment outcomes with bisphosphonates.

In conclusion, our study showed lower MCW on DPRs of patients with OI compared with children with normal BMD. The thinning of the mandibular cortex depends on the number of pamidronate cycles, the OI type, and age at the beginning of treatment, as long as it is related to the patients' phenotypes. Our results indicate that PAM alters MCW. As bisphosphonates are used in other populations, such as those with osteoporosis and bone metastases, prospective studies are necessary to

verify whether DPRs may be considered an auxiliary tool for previewing treatment outcomes in patients taking bisphosphonates.

Author Contributions

A.C. Apolinário, contributed to data acquisition, analysis, and interpretation, drafted the manuscript; P.T. Figueiredo, A.F. Leite, contributed to data acquisition, analysis and interpretation, critically revised the manuscript; A.T. Guimarães, contributed to data analysis and interpretation, critically revised the manuscript; A.C. Acevedo, contributed to conception and design, drafted the manuscript; L.M. Paula, N.S. Melo, contributed to conception and design, critically revised the manuscript; L.C. Castro, A.P. Paula, contributed to data acquisition and analysis, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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