Effects of Intravenous Pamidronate Treatment in Infants With Osteogenesis Imperfecta: Clinical and Histomorphometric Outcome

Craig FJ Munns,1,2 Frank Rauch,1 Rose Travers,1 and Francis H Glorieux1

ABSTRACT: Clinical and histomorphometric outcome was compared between children with OI who had received pamidronate since infancy and age-matched patients who had never received pamidronate. Pamidronate was associated with improved vertebral shape and mass, higher cortical width, increased cancellous bone volume, and suppressed bone turnover.

Introduction: Observations in small patient series indicate that infants with severe osteogenesis imperfecta (OI) benefit from treatment with cyclical intravenous pamidronate. However, detailed analyses of outcome are lacking for this age group.

Materials and Methods: Clinical outcome was evaluated in 29 children with OI types I (n = 3), III (n = 14), or IV (n = 12) who started pamidronate therapy before 2 years of age (age at treatment onset: median, 6 months; range, 2 weeks to 23 months) and who had completed 3 years of treatment (total annual pamidronate dose, 9 mg/kg). They were compared with a historical control group of 29 untreated children with severe OI who were matched for OI type and age at the 3-year treatment time-point. In addition, iliac bone histomorphometry was compared between 24 pamidronate-treated patients and 24 age-matched OI patients who had not received pamidronate.

Results: Morphometric evaluation of lumbar vertebrae (L1–L4) showed that the shape of vertebral bodies was better preserved in pamidronate-treated patients. This was accompanied by significantly higher lumbar spine areal and volumetric BMD (+110 and +96%, respectively) and a larger vertebral bone volume (+26%) on densitometry. Regarding mobility function, the Pediatric Evaluation of Disability Inventory gross motor score was 50% greater in the pamidronate group (p < 0.001). Iliac bone histomorphometry showed 61% higher cortical width and 89% higher cancellous bone volume in pamidronate-treated patients. Bone formation rate per bone surface in the pamidronate group was only 17% that of untreated patients.

Conclusions: In conclusion, this study suggests that cyclical pamidronate treatment started in infancy leads to improved bone strength and better gross motor function but also suppresses bone turnover markedly. It is therefore prudent to reserve pamidronate treatment to infant OI patients who present with a moderate to severe phenotype.

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Key words: bisphosphonate, bone fragility, histomorphometry, osteoporosis, pediatric

INTRODUCTION

OSTEOGENESIS IMPERFECTA (OI) is a genetic disorder with increased bone fragility and low bone mass. The most commonly used classification distinguishes four clinical types.(1) OI type I comprises patients with absence of bone deformities. Type II is lethal in the perinatal period. OI type III is the most severe form that is compatible with life. These patients have extremely short stature and limb and spinal deformities secondary to multiple fractures. Patients with mild to moderate bone deformities and variable short stature are classified as OI type IV. In the majority of patients with OI, the disease can be linked to mutations in one of the two genes coding for collagen type I α chains (COL1A1 and COL1A2).2

Cyclical intravenous therapy with the bisphosphonate pamidronate has been reported to be beneficial in children and adolescents with moderate to severe forms of OI.(3–5) Several investigators have observed that this treatment increases lumbar spine areal BMD and metacarpal cortical width, decreases fracture rate, and improves mobility.(3–5) Histomorphometric studies of iliac bone samples showed that the main effect of pamidronate treatment was to increase cortical thickness.(6) The amount of trabecular bone also increased during pamidronate therapy, because the number of trabeculae increased.

Most of the patients described in these studies were >2

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1Genetics Unit, Shriners Hospital for Children and McGill University, Montréal, Québec, Canada; 2Current Address: The Children's Hospital at Westmead; Westmead, New South Wales, Australia.
years of age when pamidronate treatment was started. In a congenital disease such as OI, it seems logical to start treatment as early as possible. Promising results have indeed been reported in severely affected OI patients who received pamidronate in the first 2 years of life.\(^{(7–11)}\) However, the scope of these observations was limited, as only nine of the reported patients were followed for >12 months. None of these reports presented information on what effects cyclical intravenous pamidronate therapy has on the bone tissue of patients who start treatment in infancy.

In this study, we describe the effects of 3 years of pamidronate therapy in OI patients who started treatment before 2 years of age and provide histomorphometric data on the treatment effect in this young age group.

**MATERIALS AND METHODS**

**Subjects**

This study was comprised of patients with a diagnosis of OI type I, III, or IV who had received pamidronate therapy at the Shriners Hospital for Children in Montreal before 2 years of age. Patients were eligible for this observational trial if they had long bone deformities or had suffered more than three fractures (including vertebral fractures).\(^{(3,7)}\) This applies to all patients with OI types III and IV and to the most severe cases of OI type I.

As per study protocol, patients underwent anthropometric, radiological, biochemical, and functional assessment at regular intervals during the study. Histomorphometric analysis was to be performed after 2 years of therapy, if feasible. To maximize the amount of histomorphometric information in this report, the criteria for including patients in these analyses were different for the anthropometric, radiological, biochemical, and functional evaluation (clinical studies) than they were for histomorphometric assessment (histomorphometric studies).

The clinical study group was comprised of all 29 OI patients who had started pamidronate treatment before 2 years of age and had completed 3 years of treatment (Table 1). *Collagen type I* mutations were found in 27 of these patients. In two patients, *no collagen type I* mutation was detectable by sequence analysis of the entire coding region. Results after 3 years of treatment were compared with those of 29 patients who were matched for OI type and age and who had not received pamidronate before the examinations reported here (Table 1). *Collagen type I* mutations were found in 19 of these patients. In one patient, no *collagen type I* mutation was detectable by sequence analysis of the entire coding region, and in nine patients the mutation testing had not been performed.

The histomorphometric study included patients who had received pamidronate treatment for at least 1 year before undergoing iliac bone biopsy. As mentioned earlier, the protocol called for bone biopsies to be performed after 2 years of treatment. However, because the biopsy specimens were preferably obtained during elective orthopedic procedures such as rodding of long bones, the actual timing of the biopsy often deviated from the treatment protocol. In patients who did not require orthopedic interventions but weighed >10 kg and did not present an elevated anesthetic risk, specimens were obtained under general anesthesia in a procedure performed exclusively for this purpose. Patients were included in this evaluation if iliac bone samples of sufficient quality were obtained.

In 49 patients, pamidronate therapy had been started before the age of 2 years and had been given for at least 1 year. At the time of this evaluation, bone biopsies had not been obtained in 17 of these patients, and in 8 patients, biopsy specimens were inadequate for analysis. Thus, 24 patients were included in this study. *Collagen type I* mutations were present in 21 of these patients. In two patients, no *collagen type I* mutation was detectable by sequence analysis, and one patient had not been tested.

Histomorphometric results in the study group were compared with those of two age-matched control groups: a cohort of children who were free from metabolic bone disorders and a group of OI patients who had not received bisphosphonate therapy before biopsy. The healthy control group was comprised of 10 children (4 girls and 6 boys) between 1.6 and 5.2 years of age, as described earlier.\(^{(3)}\) These children had undergone iliac bone biopsies during unrelated orthopedic procedures. The OI control group consisted of 24 children (age at biopsy, 1.4–5.3 years). *Collagen type I* mutations were found in 21 of these patients, in one patient, no *collagen type I* mutation was detectable by sequence analysis, and two patients had not been tested.

The study was approved by the Shriners Hospital Institutional Review Board, and informed consent was obtained from the legal guardians.

**Treatment**

Pamidronate was administered intravenously on 3 consecutive days in all patients. As previously reported, the timing and dosage of these 3-day cycles varied with age.

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because the clinical effect of a pamidronate infusion, especially on bone pain, was more short-lived in infants than in older children. Patients received 0.25 mg/kg on the first day of the first cycle, 0.5 mg/kg on days 2 and 3 of the first cycle, and 0.5 mg/kg daily on all 3 days in subsequent cycles. Cycles were repeated every 2 months. After the second birthday, treatment was continued with cycles of 0.75 mg/kg pamidronate daily on 3 successive days that were repeated every 3 months. Above 3.0 years of age, the pamidronate dose was 1 mg/kg daily for 3 days, and cycles were repeated every 4 months. Thus, the yearly dose of the drug was the same at all ages (9 mg/kg). Each dose was diluted in 0.9% saline solution and administered slowly over 4 h.

Calcium intake was maintained adequate according to the recommended daily allowance in all patients. All patients underwent physiotherapy and occupational therapy evaluation and support, including exercises and the provision of special devices for transportation and sitting. In children with significant lower limb deformity, intramedullary rodding procedures were performed when the child was able to pull up to stand. The entire multidisciplinary treatment approach has recently been described in detail.

**Anthropometry**

Height was measured using a Harpenden stadiometer (Holtain Limited, Crymych, UK). Infants and children unable to stand were measured in the supine position; others were measured standing. In cases of leg length discrepancy or contractures, the longest leg was measured. Weight was determined using digital electronic scales for infants and mechanical scales for children (Healthometer).

**Function**

Occupational therapists and physiotherapists experienced in the care of children with OI assessed the subjects before the start of pamidronate therapy and at each subsequent treatment cycle. The Pediatric Evaluation of Disability Inventory (PEDI) was used to assess gross motor and self-care abilities. Mobility was assessed using a modification of the Bleck score as follows: 0 (does not walk), 1 (able to walk during therapy sessions only), 2 (walking only within the house), and 3 (able to walk within the community).

**Radiological measurements**

All radiographs were taken using standardized techniques with a Siemens Multix H radiological unit (Siemens AG, Erlangen, Germany) onto Kodak medical film (Eastman Kodak Co., Rochester, NY, USA). Radiographs were taken as part of a skeletal survey performed at the start of pamidronate treatment and annually thereafter.

Postero-anterior radiographs of the left hand were evaluated by pediatric radiologists to calculate bone age using the method described by Greulich and Pyle. From these same radiographs, a single observer (CM) measured second metacarpal length, midshaft periosteal diameter, and endocortical diameter, as described using a dial reading caliper with a 0.04-mm resolution (General Tools). From these measurements, combined cortical thickness, cross-sectional cortical bone area, and percent cortical area were derived.

Vertebral morphometry was performed on lateral spine radiographs as described by Smith-Bindman et al. Six points were marked on each of the vertebral bodies L₁ to L₄, which corresponded to the four corners of the vertebral body and the midpoints of the end plates (Fig. 1). From these points, the anterior height, posterior height, midheight, upper length, and lower length of each vertebra was calculated. To account for magnification, all measurements were expressed relative to lower vertebral length, because this is the measure that is probably least influenced by compression fractures. All radiographs were evaluated by a single observer (CM).

**Bone densitometry**

Bone densitometry was performed in the antero-posterior direction at the lumbar spine (L₁–L₄) using a Hologic QDR 2000W or 4500A device (Hologic). Areal BMD results were transformed to age-specific z scores combining reference data from Salle et al. and data provided by the densitometer manufacturer. Volumetric BMD and bone volume were derived mathematically as described.
Biochemical measurements

Serum concentrations of total calcium, inorganic phosphate, alkaline phosphatase, creatinine, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, PTH, and TRACP, and urinary levels of the bone resorption marker cross-linked N-telopeptide of type I collagen (NTx), creatinine, and calcium were measured on fasting samples using methodology recently described. (20)

Bone biopsy and histomorphometry

Whenever possible, labeling was performed before biopsy using demeclocycline (15–20 mg/kg per day taken orally during two 2-day periods separated by a 10-day free interval). Twenty patients in the treatment group, 22 of the untreated OI patients, and all 10 children in the healthy control group completed this labeling course before the biopsy procedure. Transiliac bone samples were collected 4 or 5 days after the labeling using a Bordier trephine (5-mm core diameter) from a site located 2 cm dorsal of the anterior superior iliac spine. No side effects of this procedure were noted other than transient local discomfort.

Biopsy preparation and histomorphometric analyses were performed as described previously. (7) Bone samples were included in this analysis when cancellous bone per tissue volume was measurable. Thus, samples with a crushed cancellous compartment were excluded from analysis. Wall thickness was not measured, because reversal lines are difficult to visualize in severe OI. Consequently, activation frequency could not be determined. Osteoclast diameter was measured as the largest diameter of each cell. Mineralized cartilage was distinguished from mineralized bone on the basis of differences in staining (Fig. 2). Measurements were carried out using a digitizing table with Osteomeasure software (Osteometrics, Atlanta, GA, USA). Nomenclature and abbreviations follow the recommendations of the American Society for Bone and Mineral Research. (21)

Statistical analysis

Variables were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed data were expressed as mean and SD. Geometric means and geometric SD were calculated for nonnormally distributed variables. These variables were log-transformed before performing tests that require normal distribution. Differences between the three patient groups were tested for significance using ANOVA. Posthoc comparisons were performed using Bonferroni’s adjustment. The difference between results of treated and untreated OI patients was tested for significance using Student’s unpaired t-test. The difference in the frequency of categorical measures between the pamidronate and control groups was evaluated using the $\chi^2$ test. All tests were two-tailed, and throughout the study, $p < 0.05$ was considered significant. These calculations were performed using the SPSS software, version 11.5 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Clinical studies

In the treatment group, pamidronate therapy was started at $0.7 \pm 0.6$ (SD) years of age (range, 2 weeks to 23 months). Results after 3 years of treatment were compared with those of a control group of patients who had not received pamidronate and who were matched for OI type and age.
(Table 1). The two groups were not significantly different for height, whereas there was a trend toward an increased weight in the pamidronate group. Vertebral shape was better preserved in pamidronate-treated patients (Figs. 3 and 4). This was accompanied by significantly higher lumbar spine area and volumetric BMD (+110% and +96%, respectively) and a larger vertebral bone volume (+26%; Table 1).

After 3 years of cyclical pamidronate treatment, biochemical markers of bone turnover (alkaline phosphatase and urinary NTx/creatinine) were significantly reduced (Table 2). Serum creatinine was also slightly lower in the pamidronate cohort, whereas the other biochemical parameters were similar between the two groups.

Cortical thickness and percent cortical area of the second metacarpal bone were significantly greater after 3 years of pamidronate therapy, whereas outer bone diameter was similar between groups (Table 3). The control group had a significant delay in bone age compared with chronological age (bone age 3.2 ± 1.2 years versus chronological age 3.7 ± 1.0 years; p = 0.004). No such delay was evident in the pamidronate-treated group (bone age 3.7 ± 1.2 years versus chronological age 3.9 ± 0.8 years; p = 0.08). Fracture incidence could not be compared between the two groups because of insufficient data in the control group.

Both the PEDI gross motor score and the mobility score were significantly greater in the pamidronate group (p < 0.001; Table 4).

**Histomorphometric studies**

Results from 24 pamidronate-treated OI patients were compared with data from 24 age-matched patients who had not received pamidronate (Table 5). Quantitative histomorphometric measures in treated and untreated OI patients were also compared with a group of age-matched children without metabolic bone disease. In the treated group, pamidronate had been started at a median age of 6 months (range, 2 weeks to 23 months). Age at the time of the bone biopsy ranged from 1.6 to 5.5 years, when pamidronate had been given for 2.5 ± 0.8 years (range, 1.0–4.0 years). Anthropometric and densitometric results in patients included

![FIG. 3. Lateral lumbar spine radiographs of two children 3.3 years of age with OI type III. The child in the left panel never received pamidronate, whereas the child in the right panel received 3 years of pamidronate therapy.](image1)

![FIG. 4. Schematic representation of average vertebral body shape as determined by vertebral morphometry. Mean results for anterior height (AH), midheight (MH), and posterior height (PH) relative to lower vertebral length (see Fig. 1) are shown for the control and the pamidronate treated groups; n = 28 for the pamidronate group and n = 27 for the control group. Significant differences between corresponding measures in the two groups are indicated: *p < 0.05; **p < 0.01; ***p < 0.001.](image2)
Qualitative assessment of iliac bone specimens showed that the proportion of samples containing marrow fibrosis was significantly \( p < 0.01 \) lower in the pamidronate-treated group (8 [33%] samples) compared with untreated OI patients (18 [75%] samples). Woven bone was not detected in any of the samples. Double labels were present in all bone specimens from patients who had received two courses of tetracycline before biopsy.

External bone size (core width) was similarly low in treated and untreated OI patients (Fig. 5; Table 5). However, average cortical width and cancellous bone volume were 61% and 89% higher, respectively, in the patients who had received pamidronate (Table 5). The difference in cancellous bone volume was caused by the presence of a large number of thin trabeculae in the pamidronate group. In patients receiving pamidronate, cartilage volume on average made up 0.6% of the cancellous compartment, corresponding to 4.7% of the cancellous bone volume (Fig. 2). In contrast, only traces of cartilage were found in untreated OI patients or healthy children.

As to parameters of cancellous bone turnover, osteoid thickness was not different between the two groups of OI patients (Table 6). However, all bone surface based formation parameters were lower in the pamidronate-treated group. In particular, average bone formation rate per bone surface in the pamidronate group was only 17% that of untreated OI patients and 25% that of healthy controls. In addition, the fraction of osteoid seam length showing mineralizing activity was smaller and mineral apposition rate was lower in the treated group compared with untreated OI patients. Therefore, mineralization lag time was considerably prolonged in the treated patients.

As to bone resorption parameters, the number and surface extent of osteoclasts were not significantly different between groups. Average osteoclast diameter was similar in the pamidronate group and in OI controls (37 ± 8 versus 34 ± 4 μm; \( p = 0.12 \)). However, eroded surface was highest in children receiving pamidronate.

**DISCUSSION**

The results of this study suggest that cyclical pamidronate treatment started in infancy was associated with improvements in vertebral shape, size, and BMD, metacarpal and ilial cortical thickness, trabecular number, and gross motor function. On the down side, the treatment suppressed bone turnover and led to some accumulation of mineralized growth plate material in secondary bone.
Our structural histomorphometric findings suggest that the increase in vertebral bone mass and BMD during pamidronate treatment is mostly because of thicker cortices and a higher amount of cancellous bone. Cortical thickness also increased at the midshaft of the second metacarpal. It seems that cortical thickening at that site occurred through endocortical rather than periosteal apposition, because pamidronate-treated patients had a smaller inner bone diameter but a similar outer bone diameter than controls. We have made similar observations in iliac bone samples of older OI patients.(6)

The increase in trabecular number during pamidronate is probably caused by the effect of the drug on endochondral bone growth. Endochondral growth is normally characterized by the production of a large number of thin primary trabeculae, most of which are rapidly resorbed during the conversion of primary into secondary spongiosa.(22) Pamidronate therapy increases the number of trabeculae, presumably because fewer primary trabeculae are resorbed.(23) Because primary trabeculae are thinner than secondary trabeculae, this mechanism also may account for the observation that trabecular thickness was lower in pamidronate-treated patients.

It is plausible that thicker cortices and a higher amount of cancellous bone contribute to make vertebrae stronger. This is confirmed by the vertebral morphometry data that document improvements in vertebral shape and size, suggesting that pamidronate prevents vertebral crush fractures and allows for a more normal vertebral growth.

The results of this study suggest that pamidronate treatment of infants is associated with functional gains. Better gross motor skills and mobility may have resulted from a reduction in bone pain, lower fracture rates, and increased muscle strength, all of which have been previously associated with pamidronate treatment in OI.(3,7,8,10) These same factors may also have allowed for more active physiotherapy and occupational therapy input. It remains to be seen whether these gains will be maintained and whether they result in improved self-care and independence.

With regard to safety considerations, pamidronate treatment did not adversely affect growth rate, progression of bone age, calcium homeostasis, and renal function. However, pamidronate therapy was associated with a significant reduction in bone turnover, as indicated both by biochemical bone turnover markers and by histomorphometry. Low bone turnover may explain why more iliac bone samples

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pamidronate-treated group</th>
<th>OI control group</th>
<th>Healthy control group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (girls/boys)</td>
<td>24</td>
<td>11/13</td>
<td>12/12</td>
<td>6/4</td>
</tr>
<tr>
<td>OI types (I/III/IV)</td>
<td>24</td>
<td>4/10/10</td>
<td>5/7/12</td>
<td>—</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24</td>
<td>3.3 (1.0)</td>
<td>3.3 (1.1)</td>
<td>3.2 (1.1)</td>
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<tr>
<td>Core width (mm)</td>
<td>19</td>
<td>2.9 (1.0)</td>
<td>3.2 (1.1)</td>
<td>5.3 (1.4)</td>
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<tr>
<td>Cortical width (mm)</td>
<td>23</td>
<td>515 (240)</td>
<td>319 (151)</td>
<td>703 (277)</td>
</tr>
<tr>
<td>Bone volume per tissue volume (%)</td>
<td>24</td>
<td>14.9 (7.2)</td>
<td>7.9 (3.5)</td>
<td>17.7 (2.6)</td>
</tr>
<tr>
<td>Trabecular thickness (μm)</td>
<td>24</td>
<td>68 (18)</td>
<td>88 (23)</td>
<td>101 (11)</td>
</tr>
<tr>
<td>Trabecular number (mm)</td>
<td>24</td>
<td>2.3 (1.2)</td>
<td>1.0 (0.6)</td>
<td>1.8 (0.3)</td>
</tr>
<tr>
<td>Cartilage volume per tissue volume (%)</td>
<td>24</td>
<td>0.6 (0.0–11.1)</td>
<td>0.0 (0.0–0.6)</td>
<td>0.0 (0.0–0.0)</td>
</tr>
<tr>
<td>Cartilage volume per bone volume (%)</td>
<td>24</td>
<td>4.7 (0.0–35.4)</td>
<td>0.0 (0.0–0.6)</td>
<td>0.0 (0.0–1.2)</td>
</tr>
</tbody>
</table>

Values are mean (SD) unless otherwise indicated. p values represent the significance of the difference between the three groups (ANOVA).

* Median (range) is given, and the p value is calculated by Kruskal-Wallis test.

The results of the posthoc test (Bonferroni adjustment) between individual groups: † significant difference (p < 0.05) to pamidronate-treated group; ‡ significant difference (p < 0.05) to OI control group; § significant difference (p < 0.05) to healthy group.
Bone resorption and bone formation reflect resorptive function. Similarly, the elevated read-
and therefore it is likely that the osteoclast counts do not render osteoclasts dysfunctional without causing apoptosis,
ferences between groups. In addition, pamidronate may numbers may be required to find statistically significant dif-
large interindividual variability. Therefore, larger sample
tients did not have significantly lower osteoclast numbers

growth plate cartilage might cause bone fragility. We have no indication at present that the increased amount of calcified cartilage caused clinical problems in our pa-

Similar to our previous histomorphometric studies in older OI patients, none of the participants of this study had signs of a mineralization defect. Mineralization lag time was prolonged during therapy, but there was no accumula-

difficulty, age at onset of treatment, predicted collagen mutation and

This study would not have been possible without the tremen-
dous support of the nursing staff and the departments of occupational therapy and physiotherapy at the Shriners Hospital for Children. The authors thank Guy Charette and Josée Dépot for technical assistance with biopsy sample processing and Mark Lepik for preparing the figures. We are indebted to Dr Peter Roughley and Dr Liljana Lalic for performing sequence analyses. This study was supported by the Shriners of North America.

REFERENCES


Table 6. Histomorphometric Parameters of Cancellous Bone Turnover

<table>
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<tr>
<td></td>
<td>n</td>
<td></td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Bone formation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoid thickness (μm)</td>
<td>24</td>
<td>4.7 (0.9)</td>
<td>24</td>
<td>5.1 (1.7)</td>
</tr>
<tr>
<td>Osteoid surface per bone surface (%)</td>
<td>24</td>
<td>33 (13)</td>
<td>24</td>
<td>48 (14)</td>
</tr>
<tr>
<td>Osteoblast surface per bone surface (%)</td>
<td>24</td>
<td>6.2 (2.4)</td>
<td>24</td>
<td>19.6 (1.8)</td>
</tr>
<tr>
<td>Mineralizing surface per bone surface (%)</td>
<td>20</td>
<td>5.6 (4.9)</td>
<td>20</td>
<td>24.8 (9.1)</td>
</tr>
<tr>
<td>Mineralizing surface per osteoid surface (%)</td>
<td>20</td>
<td>17 (12)</td>
<td>21</td>
<td>53 (20)</td>
</tr>
<tr>
<td>Mineral apposition rate (μm/day)</td>
<td>19</td>
<td>0.57 (0.14)</td>
<td>22</td>
<td>0.77 (0.17)</td>
</tr>
<tr>
<td>Mineralization lag time (day)</td>
<td>19</td>
<td>62 (2.8)</td>
<td>19</td>
<td>14 (1.7)</td>
</tr>
<tr>
<td>Bone formation rate per bone surface (μm³/μm²/y)</td>
<td>19</td>
<td>12 (9)</td>
<td>21</td>
<td>70 (31)</td>
</tr>
<tr>
<td>Bone resorption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoclast number per bone perimeter (#/mm)</td>
<td>24</td>
<td>0.49 (2.0)</td>
<td>21</td>
<td>0.37 (2.1)</td>
</tr>
<tr>
<td>Osteoclast surface per bone surface (%)</td>
<td>24</td>
<td>1.6 (1.1)</td>
<td>21</td>
<td>1.4 (1.1)</td>
</tr>
<tr>
<td>Eroded surface per bone surface (%)</td>
<td>24</td>
<td>30 (14)</td>
<td>23</td>
<td>22 (10)</td>
</tr>
</tbody>
</table>

Values are mean (SD).

*Geometric mean [geometric SD] are given. p values represent the significance of the difference between the three groups (ANOVA).

The results of the posthoc test (Bonferroni adjustment) between individual groups: †significant difference (p < 0.05) to pamidronate-treated group; ‡significant difference (p < 0.05) to OI control group; §significant difference (p < 0.05) to healthy control group.

contained calcified cartilage during pamidronate treatment. Growth plate cartilage probably is not completely removed during the conversion of primary to secondary spongiosa when turnover is low. It has been suggested that this residual growth plate cartilage might cause bone fragility. We have no indication at present that the increased amount of calcified cartilage caused clinical problems in our pa-

This highlights the requirement for close monitoring of in-


disability years or even decades later. It is therefore prudent to reserve pamidronate treatment to infant OI patients who present with a moderate to severe phenotype.

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