

Cyclical Intravenous Pamidronate Treatment Affects Metaphyseal Modeling in Growing Patients With Osteogenesis Imperfecta

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ABSTRACT: This analysis of 50 growing patients with osteogenesis imperfecta revealed that 2–4 years of pamidronate treatment lead to abnormalities in the shape of the distal femoral metaphyses.

Introduction: Cyclical intravenous pamidronate therapy is of clinical benefit in children and adolescents with moderate to severe osteogenesis imperfecta (OI) but might interfere with the shaping of long bone metaphyses during growth.

Materials and Methods: We evaluated the distal femur in 50 growing children with moderate to severe OI (mean age, 6.7 ± 3.4 years; 26 girls) who had received 2–4 years of pamidronate therapy (annual dose, 9 mg/kg body weight). The mediolateral width of the distal femoral growth plate and of the metaphysis, as well as the ratio between these two measures (called metaphyseal index), were determined on lower limb radiographs.

Results: Compared with untreated OI patients who were matched for OI type and age, pamidronate-treated patients had similar growth plate width but wider metaphyses, resulting in a 26% higher metaphyseal index ($p < 0.001$). Apart from the effect on bone shape, each pamidronate cycle induces a transverse line in metaphyses that are adjacent to active growth plates. Analyses of these transverse lines revealed that they persist for an average time of ~4 years, with a range from 2 to 8 years.

Conclusions: Pamidronate interferes with the process of periosteal resorption that is normally responsible for shaping the distal femoral metaphysis. Pamidronate-induced transverse lines disappear with time, supporting the view that these lines represent horizontal trabeculae that undergo remodeling. There is no evidence at present that these treatment induced morphological changes have any clinical implications.

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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 having OI type IV. In the majority of patients with OI, the disease is linked to mutations in one of the two genes encoding collagen type I α chains.

Cyclical intravenous therapy with the bisphosphonate pamidronate has been reported to be beneficial in children and adolescents with moderate to severe forms of OI. Several investigators have observed that this treatment increases the density and size of lumbar vertebral bodies, decreases fracture rate, and improves mobility.⁽¹⁾

Bisphosphonates act on the skeleton mainly by inhibiting bone resorption. During longitudinal growth, the periosteal surfaces of long-bone metaphyses are sites of high resorptive activity.⁽²⁾ As the growth plate proceeds in a direction away from the center of the bone, the newly created metaphyseal bone continues to decrease its diameter by periosteal resorption until it has reached the cross-sectional size of the diaphysis.⁽³⁾ This metaphyseal inwaisting process is thus linked to longitudinal growth and is part of the modeling of the skeleton during childhood and adolescence. It is known from animal experiments that bisphosphonates given in high doses interfere with metaphyseal inwaisting.⁽⁴⁾ A similar observation has been made in a boy who received excessive doses of pamidronate.⁽⁵⁾ In contrast, a recent report suggested that pamidronate in currently used doses does not affect the metaphyseal shape of growing children.⁽⁶⁾

Cyclical pamidronate may not only affect the outer shape but also the inner structure of the growing metaphysis. As long as longitudinal growth continues, each pamidronate infusion cycle leaves a dense line at the interface between growth plate and metaphysis.⁽⁷⁾ As the growth plate moves

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on, these lines remain visible radiologically as metaphyseal transverse lines. These lines may correspond to transverse trabeculae that undergo remodeling.⁽⁸⁾ If so, they should disappear with time, because remodeling should realign the trabeculae to a more normal orientation.⁽⁹⁾ Currently there is no information about how long these treatment lines persist.

In this study, we investigated the effects of intravenous pamidronate treatment on metaphyseal bone development in children and adolescents with OI. Metaphyseal inwaisting and the persistence of transverse lines were evaluated in the distal femur. Results were compared with the activity of bone turnover, as estimated from histomorphometric analyses of iliac crest bone samples.

MATERIALS AND METHODS

Subjects

The main study cohort comprised children and adolescents with OI types I, III, and IV who received pamidronate therapy at the Shriners Hospital for Children in Montreal, Canada, for at least 2 years. Patients who were diagnosed with OI types V, VI, and VII according to our expanded classification were not included in this evaluation.⁽¹⁾ Patients were eligible for pamidronate treatment if they had long bone deformities or had suffered three or more fractures per year (including vertebrae) during the previous 2 years. This applies to all patients with OI types III and IV and generally to the more severe cases of OI type I. Patients were included in this study if adequate radiographic images of a distal femur were available at the start of pamidronate treatment and after a treatment period of 2–4 years.

Of the 111 patients with OI types I, III, and IV who had received at least 2 years of pamidronate treatment at our institution, adequate radiographic documentation was available in 66. Because metaphyseal inwaisting is a growth-dependent process, this patient group was subdivided according to growth status, as judged by the appearance of the distal femoral growth plate on the second radiograph. Fifty patients (26 girls, 24 boys; OI type I, $n = 8$; OI type III, $n = 14$; OI type IV, $n = 28$) still had clearly open growth plates and are referred to as the “growing group.” In seven patients (three girls and four boys; age at baseline 10.8–15.2 years; mean age, 13.0 years; OI type I, $n = 3$; OI type IV, $n = 4$), fused growth plates were present on the follow-up X-ray. Nine patients had the severe changes referred to as “popcorn” metaphyses (seven girls and two boys; age at baseline, 3.4–16.7 years; mean age, 8.0 years; OI type III, $n = 5$; OI type IV, $n = 4$). The two latter groups were analyzed separately.

Distal femoral metaphyses were also evaluated in 72 OI patients (35 girls and 37 boys; age range, 0.1–15.3 years; OI type I, $n = 13$; OI type III, $n = 18$; OI type IV, $n = 41$) who had not received medical treatment and who did not have popcorn metaphyses. Fifty of these patients (OI type I, $n = 8$; OI type III, $n = 14$; OI type IV, $n = 28$) could be matched with the 50 patients of the growing group on the basis of OI type and age. Results of these matched controls were compared with those of the growing group after 2–4 years of pamidronate treatment.

The persistence of transverse lines was limited to patients of the growing group, because these lines arise only in bones with active growth plates. The most current proximal tibia radiograph obtained during pamidronate treatment was evaluated in patients who had received at least 4 years of therapy. Adequate radiographs were available in 43 patients (age at radiograph, 10.0 ± 3.7 years; OI type I, $n = 7$; OI type III, $n = 16$; OI type IV, $n = 20$).

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

Treatment

Pamidronate was administered intravenously on 3 consecutive days in all patients. As described in detail elsewhere, the timing and dosage of these 3-day cycles varied with age, but the yearly dose of pamidronate remained at 9 mg/kg throughout the treatment period.⁽¹⁾ Calcium intake was maintained adequate according to the recommended daily allowance. All patients underwent standard physiotherapy, occupational therapy programs, and orthopedic care as required.

Anthropometric and biochemical measurements

Height was measured using a Harpenden stadiometer (Holtain, Crymych, UK). Weight was determined using digital electronic scales for infants and mechanical scales for children (Healthometer, Bridgeview, IL, USA). Height and weight measurements were converted to age- and sex-specific Z scores on the basis of reference data published by the Centers for Disease Control and Prevention.⁽¹⁰⁾ Urinary cross-linked N-telopeptides of type I collagen (NTx) was quantified by enzyme-linked immunosorbent assay (Osteomark; Ostex International, Seattle, WA, USA) using the second void sample of the morning.

Radiological analyses

Metaphyseal inwaisting was evaluated on posterior-anterior lower limb radiographs as described by Ward et al.⁽⁶⁾ The width of the distal femoral growth plate was determined in the medio-lateral direction using a dial reading caliper (General Tools, New York, NY, USA). Metaphyseal width was measured at a site whose distance to the growth plate corresponded to one-half of growth plate width (Fig. 1). The left femur was evaluated in all but seven patients, in whom a recent fracture or suboptimal quality of one of the radiographs made the analysis of the left side unreliable. All radiographs were taken with a film focus distance of 120–180 cm, resulting in a maximum magnification error of <10%.

The persistence of pamidronate-induced transverse lines was evaluated on posterior-anterior radiographs of the proximal tibia. This site was chosen because the 2-D projection of each line is more concise and therefore easier to determine in bones that are smaller than the femur. The transverse line with the greatest distance to the growth plate represents the “oldest” visible line. The date of the treatment cycle corresponding to this line was determined by comparing the total number of visible lines with the

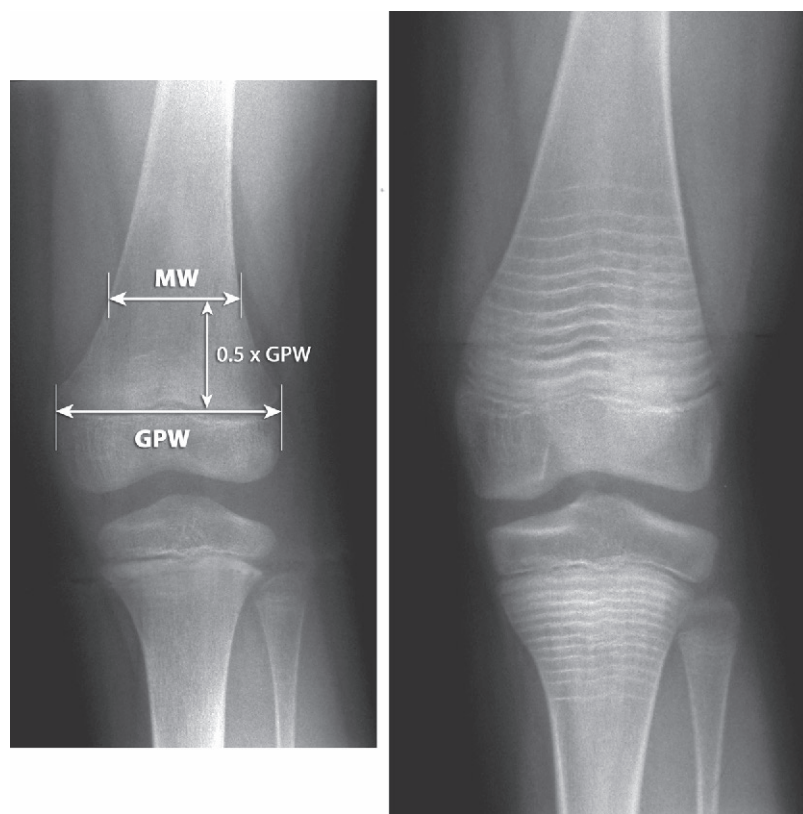


FIG. 1. Distal femoral metaphyseal width (MW) was measured at a site whose distance to the growth plate corresponded to one-half of growth plate width (GPW). The metaphyseal index was calculated as the ratio between metaphyseal and growth plate width. Shown are radiographs of a boy with OI type I that were taken at the start of pamidronate treatment (left; age 7.3 years; metaphyseal index, 0.59) and 3.6 years later, when 11 pamidronate cycles had been given (right; metaphyseal index, 0.72). Note that all expected 11 transverse lines are visible in the proximal tibial metaphysis as well as in the distal femur.

dates of the treatment cycles that a patient had received. In that manner, the “age” of the oldest radiographically visible treatment line could be calculated.

DXA was performed in the anterior-posterior direction at the lumbar spine (L_1 – L_4) using a Hologic QDR 2000W or 4500 device (Hologic, Waltham, MA, USA). Areal BMD results were transformed to age-specific Z scores combining reference data from Salle et al.⁽¹¹⁾ and data provided by the densitometer manufacturer.

Bone biopsy and histomorphometry

Results of the metaphyseal analyses in the growing group were compared with histomorphometric results of iliac bone biopsy samples that had been obtained within a year of the last radiograph. For comparison with the metaphyseal index, biopsy samples were available from 38 patients, 37 of whom had received tetracycline double labeling for dynamic histomorphometry. For the analysis of transverse metaphyseal lines, biopsy samples were available from 40 patients. The samples had been obtained after 3.0 ± 1.1 (SD) years of pamidronate treatment from a site 2 cm posterior to the superior anterior iliac spine. Biopsy preparation and histomorphometric analyses were performed as previously described.⁽¹²⁾ Nomenclature and abbreviations follow the recommendations of the American Society for Bone and Mineral Research.⁽¹³⁾

Statistics

Differences in cross-sectional comparisons between groups were tested for significance using unpaired *t*-tests or

Mann-Whitney tests, as appropriate. Paired *t*-tests were used to analyze the longitudinal changes during pamidronate treatment. All tests were two-tailed, and throughout the study, $p < 0.05$ was considered significant. Associations are given as Pearson correlation or Spearman rank correlation, as appropriate. Differences between different types of OI at baseline or during pamidronate treatment were tested for significance using ANOVA with Bonferroni's adjustment for multiple comparisons. These calculations were performed using the SPSS software, version 11.5 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Metaphyseal inwaisting

In OI patients not receiving medical therapy, the metaphyseal index decreased with age (Fig. 2), indicating that developmental changes made the distal femoral metaphysis more slender.

Pamidronate-treated patients in the growing group grew at a yearly rate ranging from 3.8 to 13.1 cm (median, 6.0 cm), which maintained average height Z scores constant (Table 1). Lumbar spine areal BMD and urinary NTx levels showed the expected changes during pamidronate therapy. During treatment, average mediolateral growth plate and metaphyseal widths increased by 32% and 59%, respectively, leading to a significant increase in the metaphyseal index (Table 1).

This rise in the metaphyseal index is the opposite of what is observed in untreated OI patients (Fig. 2). Indeed, after

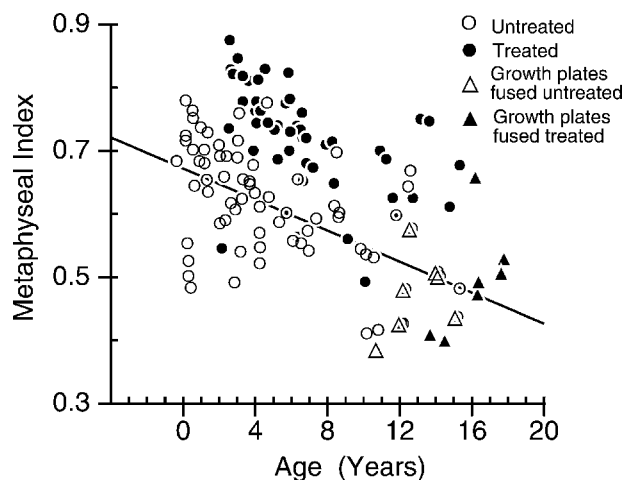


FIG. 2. Relationship between the metaphyseal index and age in children with OI. The regression line indicates the association of these parameters in the untreated patients ($N = 72$; metaphyseal index = $0.672 - 0.012 \times \text{age}$; $r^2 = 0.35$; $p < 0.001$).

2–4 years of pamidronate treatment, 47 of the 50 patients in the growing group (94%) had a metaphyseal index above the regression line for untreated patients (Fig. 2). Compared with matched untreated control patients, the growing group had similar growth plate width but higher metaphyseal width (Table 1). This resulted in a 26% higher metaphyseal index in the treated group. In 31 patients of the growing group, further radiographic follow-up was available up to an average treatment time of 5.5 ± 1.1 years. No further increase in metaphyseal index was noted ($p = 0.94$).

As can be appreciated from Fig. 2, metaphyseal index varied over a wide range in growing patients who had received pamidronate. We therefore attempted to elucidate predictors of the metaphyseal index changes after 2–4 years of treatment. No differences in metaphyseal index were found between the sexes ($p = 0.58$) or between OI types ($p = 0.94$), and there was no significant association between the metaphyseal index and urinary NTx excretion. However, the metaphyseal index was negatively associated with age ($r = -0.49$; $p < 0.001$; Fig. 2), and there was also a positive association with height velocity (Fig. 3). In addition, the metaphyseal index was negatively correlated with both bone formation rate per bone surface ($n = 37$; $r = -0.47$; $p = 0.002$) and the number of osteoclasts per bone perimeter ($n = 38$; $r = -0.38$; $p = 0.009$), as determined in the cancellous compartment of transiliac bone biopsy samples.

In patients who had fused distal femoral growth plates at follow-up, no changes in metaphyseal index were noted during pamidronate therapy (change from baseline, $+0.02 \pm 0.05$; $p = 0.43$). Similarly, pamidronate had no effect on the metaphyseal index in patients with popcorn epiphyses ($n = 9$; change from baseline, -0.03 ± 0.09 ; $p = 0.36$).

Transverse metaphyseal lines

Transverse metaphyseal lines were evaluated on X-rays of growing patients who had received an average of 5.5

years (range, 4.0–8.2 years) of pamidronate treatment. Although these patients had undergone 18.7 treatment cycles on average (range, 11–26), only a mean of 13.0 (range, 6–23) transverse lines were visible on radiographs of the proximal tibia. Thus, treatment lines must have disappeared with time. The age of the oldest treatment line ranged from 2.0 to 7.9 years (mean, 4.1 years). The length of treatment line persistence was not associated with sex, age, or height gain during pamidronate treatment ($p > 0.10$ in each case). However, urinary NTx tended to be higher in patients whose treatment line persistence was shorter ($r = -0.26$; $p = 0.07$). The persistence of transverse lines was also negatively associated with the number of osteoclasts per bone perimeter in biopsy samples ($n = 40$; $r = -0.26$; $p < 0.05$).

DISCUSSION

This study suggests that pamidronate at currently used doses can affect metaphyseal modeling in OI patients. This effect is clearly growth dependent, because it was observed only in patients who had active growth plates but not in patients with fused or disintegrated (“popcorn metaphyses”) growth plates.

Factors that influence the geometry of the distal femoral metaphysis and thus the metaphyseal index during growth are as shown in Fig. 4: the rate of bone elongation at the growth plate; the speed of growth plate widening in the mediolateral direction; the speed of metaphyseal inwaisting; and the diameter of the diaphysis. Dynamic histomorphometric studies have not found evidence that pamidronate influences periosteal apposition.⁽¹⁴⁾ It thus seems likely that pamidronate mostly affects the third of these factors. A decreased speed of inwaisting combined with unchanged longitudinal growth inevitably leads to an increase in the diameter of the metaphysis, as was found in this study.

Our results differ from those of a recent cross-sectional study that examined metaphyseal inwaisting in a cohort of 20 children who received pamidronate to treat conditions other than OI.⁽⁶⁾ It was concluded that pamidronate given at a similar yearly dose as in our patients did not interfere with metaphyseal inwaisting. The reasons for the discrepancy between the two studies are not immediately clear. The earlier analysis certainly had less power than the present one to detect metaphyseal abnormalities because of the cross-sectional design, smaller study population, and shorter treatment duration (average of 1.35 years compared with 2.9 years in our study). However, it is also possible that the metaphyseal periosteum of OI patients is more sensitive to pamidronate than that of other patients.

In healthy children, the metaphyseal index reportedly remains constant after 5 years of age,⁽⁶⁾ whereas we noted a decrease with age in our group of untreated OI patients. It thus seems that the disease process as such has some effect on metaphyseal modeling in OI. These data do not allow judging of which of the determinants of metaphyseal geometry are responsible for these differences between healthy and OI bones.

The effect of pamidronate on metaphyseal modeling

TABLE 1. CLINICAL CHARACTERISTICS AND RESULTS OF METAPHYSEAL ANALYSES IN 50 GROWING OI PATIENTS RECEIVING PAMIDRONATE (GROWING GROUP) AND IN 50 UNTREATED OI PATIENTS (CONTROL GROUP)

	Growing group		<i>p</i> *	Control group	
	Baseline	2–4 years PAM		Baseline	<i>p</i> †
Age (years)	3.8 ± 3.4	6.7 ± 3.4		6.6 ± 4.1	0.92
Height (Z score)	−4.0 ± 2.5	−4.1 ± 3.8	0.66	−4.3 ± 2.5	0.73
Weight (Z score)	−2.2 ± 1.6	−1.7 ± 1.6	0.03	−2.4 ± 1.4	0.03
Areal BMD (Z score)	−5.7 ± 1.2	−2.0 ± 1.2	<0.001	−5.4 ± 1.2	<0.001
NTx/creatinine (nmol/mmol)	944 ± 379	326 ± 98	<0.001	755 ± 296	<0.001
Growth plate width (cm)	3.7 ± 1.4	4.9 ± 1.3	<0.001	4.8 ± 1.8	0.77
Metaphyseal width (cm)	2.2 ± 0.8	3.5 ± 0.9	<0.001	2.6 ± 0.8	<0.001
Metaphyseal index	0.63 ± 0.08	0.72 ± 0.08	<0.001	0.57 ± 0.11	<0.001

Values are mean ± SD.

* Result of paired *t*-test between result at baseline and after 3 years of pamidronate treatment in the growing group.

† Result of unpaired *t*-test between result after 3 years of pamidronate treatment in the growing group and the control group.

PAM, pamidronate.

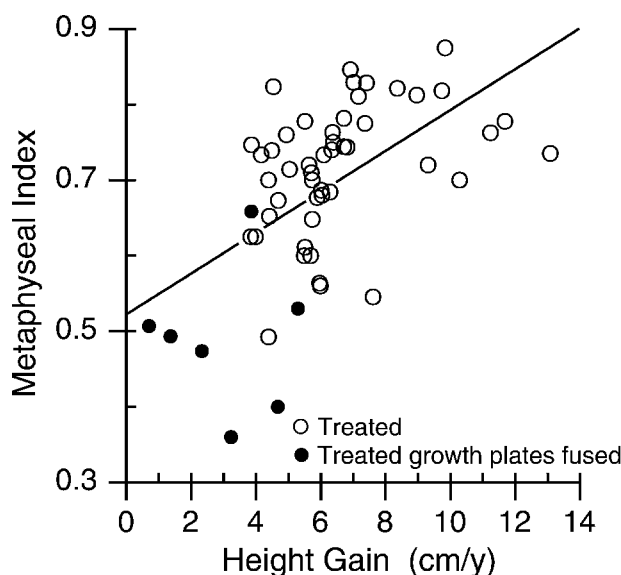


FIG. 3. Relationship between the metaphyseal index and height velocity during 2–4 years of pamidronate treatment (metaphyseal index = $-2.21 + 11.78 \times \text{height velocity}$; $r^2 = 0.31$; $p < 0.001$).

should correlate with the extent to which bone resorption is suppressed. A more severe inhibition of bone modeling should lead to a more pronounced slowdown in metaphyseal inwaisting and thus to a higher metaphyseal index (at least if longitudinal growth is not affected). In accordance with this hypothesis, we found that histomorphometric parameters of bone turnover were negatively correlated with the metaphyseal index. Even though these histomorphometric data do not directly indicate what is going on in the metaphysis of the distal femur, they likely reflect a systemic treatment effect. However, the response of cortical bone metabolism to pamidronate treatment is probably less pronounced and more varied than that of cancellous bone remodeling.⁽¹⁴⁾ This may explain why metaphyseal shaping exhibited a large variability among patients receiving pamidronate.

Apart from changes in metaphyseal modeling, cyclical

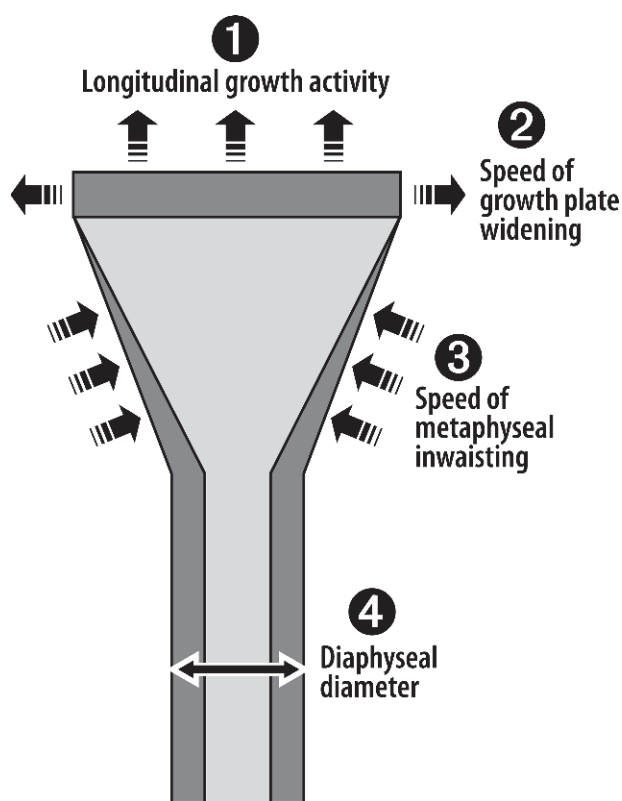


FIG. 4. Factors determining the dynamics of metaphyseal shaping during growth. Pamidronate treatment decreases the speed of metaphyseal inwaisting by interfering with periosteal resorption.

pamidronate treatment of growing patients also induces radiographically apparent transverse metaphyseal lines. These lines probably correspond to horizontal trabeculae that may arise through similar mechanisms as the so called “growth arrest,” or Harris lines.⁽⁸⁾ When growth plate activity is temporarily interrupted, osteoblasts start to deposit bone matrix on the metaphyseal site of the growth plate. When growth resumes, the growth plate moves away from this newly created horizontal trabecula, which becomes visible radiographically.⁽¹⁵⁾

We observed that these lines remain visible for ~4 years on average. This finding is in accordance with the concept that they undergo normal remodeling.⁽⁸⁾ Interestingly, transverse lines tended to persist longer in children whose histomorphometric indicators and biochemical markers of bone resorption were lower. This indicates that a low remodeling activity contributes to the persistence of the transverse lines during pamidronate treatment.

The clinical consequences of these pamidronate-induced metaphyseal changes are unclear at present. Because the amount of trabecular bone is usually very low in moderately to severely affected patients with OI,⁽¹⁶⁾ it may be preferable to increase bone mass in the metaphyses to improve the mechanical properties of the long bones. Accordingly, it can be hypothesized that these transverse lines add support to the metaphyses.

In conclusion, this study shows that intravenous pamidronate treatment interferes with the process of periosteal resorption that is normally responsible for shaping the distal femoral metaphysis during growth. At present, there is no evidence that this adverse event is of clinical significance.

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