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Long-bone changes after pamidronate discontinuation in children and adolescents with osteogenesis imperfecta

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Abstract

Cyclical intravenous pamidronate is a widely used symptomatic therapy in moderate to severe osteogenesis imperfecta (OI). The effects of treatment discontinuation on long bone development have not been characterized. In this observational study we used peripheral quantitative computed tomography to assess the radius at the distal metaphysis and at the diaphysis in 23 young OI patients (11 female) who had received pamidronate for at least 3 years. Measurements were performed twice, at the time of treatment discontinuation (when the age of the patients ranged from 5.9 to 21.3 years) and at an average of 1.9 years (range 1.5 to 2.4 years) later. At the time of pamidronate discontinuation, all but one of the patients who were below 15 years of age ($n=14$) had a positive age- and sex-specific z-score for bone mineral content (BMC) at the metaphysis, resulting in a mean z-score of +2.0 (SD=1.0) for this subgroup. In contrast, patients aged 15 years or older ($n=9$) had an average metaphyseal BMC z-score of −1.5 (SD=1.5). After pamidronate discontinuation, metaphyseal BMC z-score decreased by an average of 2.4 (SD=2.0) in the whole group. The change in BMC z-score was growth-dependent, as BMC z-scores decreased by about 2 or more in all patients in whom distal radius growth plates were open when pamidronate was discontinued. In contrast, none of the 11 patients with closed distal radius growth plates experienced a decrease in metaphyseal BMC z-score by more than 2. At the diaphysis, the average BMC z-score was low at the time of the last pamidronate infusion [z-score −1.7 (SD=1.4)]. After pamidronate discontinuation, the average diaphyseal BMC z-score decreased by only 0.3 (SD=0.4). In summary, this study shows that the effect of pamidronate discontinuation is much larger at the radial metaphysis than at the diaphysis and is dependent on growth. Metaphyseal bone tissue added by longitudinal growth after treatment discontinuation has a lower density than tissue created during treatment. It is possible that this produces zones of localized bone fragility after pamidronate treatment is stopped in growing children.
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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 in children surviving the neonatal time. 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 encoding collagen type I alpha chains (*COL1A1* and *COL1A2*) [1]. Recently three disease entities (named OI types V, VI and VII) have been identified that have a similar phenotype as the other types of OI but are not associated with collagen type I mutations [1].

Cyclical intravenous treatment with the bisphosphonate pamidronate has a beneficial effect in children and adolescents with severe OI [1]. It has been reported that this treatment increases lumbar spine bone mineral density (BMD) and metacarpal cortical width, decreases fracture rates and improves mobility [1–3]. Pamidronate is now used worldwide to treat children and adolescents with moderate to severe forms of OI.

Nevertheless, it is unclear for how long pamidronate treatment should be continued. One might argue that, as OI is a lifelong disorder, the symptomatic treatment with pamidronate should never be stopped. On the other hand, there is lingering concern about the long-term consequences of the treatment. Bisphosphonates are buried in the skeleton where they have a

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half-life of many years [4]. Any adverse effects that might arise from the presence of the drug in the bones may therefore manifest late and persist for a long time.

Given the fact that the long-term consequences of the treatment during the growing years are unknown, it may be desirable to limit the exposure of young OI patients to pamidronate. In a previous study, we therefore evaluated the effects of treatment discontinuation in young OI patients who had received pamidronate treatment for several years [5]. This showed that the gains in lumbar spine bone mass that had been achieved during pamidronate therapy were maintained for at least 2 years after treatment discontinuation, but that increases in lumbar spine areal BMD lagged behind that of healthy subjects. We also reported that the effects of treatment discontinuation were more pronounced in growing patients than in those who had achieved final height.

These previous observations were limited to the evaluation of bone mass changes at the lumbar spine and did not provide information on changes in long bones. In the present study we therefore examined the effects of pamidronate discontinuation on the radius using peripheral quantitative computed tomography (pQCT).

Subjects and methods

Subjects

This observational study comprised patients with a diagnosis of OI type I, III or IV who had received pamidronate at the Shriners Hospital for Children in Montreal. Patients were eligible for pamidronate treatment if they had long-bone deformities or had suffered two or more fractures per year (including vertebrae) in the 2 years prior to starting therapy. The present analysis does not include patients who fulfilled the Sillence criteria for OI type IV, but who could be further classified as having OI type V, VI or VII on the basis of our expanded classification [1]. The study was approved by the Shriners Hospital Institutional Review Board, and informed written consent was obtained from patients and/or legal guardians, as appropriate.

This study included patients who had received pamidronate for a minimum period of 3 years and had a follow-up period after treatment discontinuation of at least 18 months. All of these subjects had also been included in an earlier report on lumbar spine bone density changes after pamidronate discontinuation [5]. To be part of the present analysis, patients had to be able to undergo pQCT analysis at the two time points of the present analysis. This requires a forearm of sufficient length (at least 18 cm) that is free of metal (such as intramedullary rods). In addition, the patient must be able to hold the arm still for the duration of the measurement (approximately 2 min). Peripheral QCT could not be performed at the lower extremity in these patients, as most had undergone intramedullary rodding procedures of both tibias and femurs.

Twenty-three patients (11 females, 12 males) were included in this study. The diagnostic distribution was as follows: OI type I, $n=3$; OI type III, $n=2$; OI type IV, $n=18$. Collagen type I mutations were found in 21 of these patients. In two patients no collagen type I mutation was detectable by sequence analysis of the coding regions of the *COL1A1* and *COL1A2* genes, but a diagnosis of OI was made on the basis of typical clinical findings (dentinogenesis imperfecta, blue sclera).

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 and occupational therapy programs and orthopedic care, as required.

Anthropometric measurements

Height was measured using a Harpenden stadiometer (Holtain Limited, Crymych, UK). Weight was determined using mechanical scales (Healthometer, Bridgeview, USA). Height and weight measurements were converted to age- and sex-specific *z*-scores based on reference data published by the Centers for Disease Control and Prevention [6]. Forearm length was measured at the non-dominant forearm as the distance between the ulnar styloid process and the olecranon.

Dual-energy X-ray absorptiometry

Dual-energy X-ray absorptiometry (DXA) was performed in the antero-posterior direction at the lumbar spine (L1–L4) using a Hologic QDR Discovery device (Hologic Inc., Waltham, MA). An estimate of three-dimensional BMD (unit mg/cm^3), commonly called volumetric BMD in the field of bone densitometry, was derived by calculating the ratio between bone mineral content (BMC, the total amount of mineral in the four measured vertebrae) and the extrapolated external volume of the measured bones. This was done as described by Carter et al. [7] using the formula:

$$\text{Volumetric BMD} = (\text{BMC})/(\text{projectionarea})^{1.5}$$

DXA results were compared to reference data that are based on a study of Canadian children [8].

Peripheral quantitative computed tomography

Peripheral QCT was performed at the radius using the Stratec XCT2000® equipment (Stratec Inc., Pforzheim, Germany). Measurements were preferably performed at the non-dominant forearm, but the dominant forearm was analyzed when there was a recent fracture (less than 1 year before the pQCT analysis) on the non-dominant side. Two sites were assessed, representing metaphyseal and diaphyseal bone, respectively, as described [9,10].

For the analysis of the radial metaphysis, the scanner was positioned on the distal forearm and a coronal computed radiograph (scout view) was carried out. The scout view was used to determine the position of a 'reference line'. In patients with an open growth plate, the reference line was drawn through the most distal portion of the growth plate. When the growth plate was no longer visible, the reference line was drawn through the middle of the ulnar border of the articular cartilage. The measurement was performed at a site whose distance to the 'reference line' corresponded to 4% of forearm length ('4% site'). A single tomographic slice of 2.0 mm thickness was taken at a voxel size of $0.4\times0.4\times2$ mm. The speed of the translational scan movement was set at 20 mm/s. Image acquisition, processing and the calculation of numerical values were performed using the manufacturer's software package (version XCT 5.50D). The outer bone contour was detected at the default threshold of 280 mg/cm^3. Parameters at that site were calculated using the software's CALCBD routine.

The radial diaphysis was analyzed at a site whose distance to the ulnar styloid process corresponded to 65% of forearm length ('65% site'). Parameters for voxel size, slice thickness and scan speed were the same as for the metaphyseal measurement. The cortex of the radial diaphysis was analyzed at a threshold of 710 mg/cm^3 using the software's CORTBD routine. The Strength–Strain Index was determined at a threshold of 480 mg/cm^3.

The main parameters of pQCT analysis at the radius were BMC (corresponding to the amount of mineral per mm cross-sectional slice thickness), total volumetric BMD (volumetric BMD averaged across the entire bone cross-section), total cross-sectional area (the surface area of the entire bone cross-section, including cortex and marrow space), Strength–Strain Index (an estimate of torsional bone strength), as well as trabecular and cortical volumetric BMD. Results of pQCT analyses were compared to the findings in a reference population of healthy children and adolescents, which has been previously described [9]. This cohort comprised 371 healthy children and

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