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Quantification of metaphyseal modeling in children treated with bisphosphonates

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Abstract

There has been recent concern in the literature that the treatment with bisphosphonates in children can have an adverse effect on metaphyseal modeling leading to "drug-induced osteopetrosis". We created a normal database called metaphyseal index in the distal femur so that we could quantify the inwasting modeling process in children on bisphosphonates.

Radiographs of the distal femur of 468 normal children who had presented to our institution for orthopedic trauma were examined. A measurement of the distal femoral growth plate width (GPW) was recorded. The femoral width at an interval of 0.5 GPW proximal to the distal femoral growth plate was also recorded (0.5 W). The metaphyseal index was defined as a ratio of 0.5 W/GPW. A graph of the means, one and two standard deviations from the mean, was constructed using the data obtained from this cohort.

We found this ratio to be constant with minimal variability regardless of the age or sex of the child. We plotted 20 patients at our institution given bisphosphonates for localized orthopedic complaints. *Z* scores for girls averaged 0.68 and boys 0.13. Three patients had *Z* scores >2.0, with values of 2.2, 2.9, and 3.2.

Metaphyseal modeling in the distal femur is constant, with slight variation between sexes, resulting in a similar shape of the distal femur throughout childhood. Clinically relevant doses of bisphosphonates given for appropriate indications do not necessarily disturb this process, while the beneficial clinical effect is maintained.

Keywords: Bisphosphonates; Bone modeling; Pediatrics; Radiology; Bone development

Introduction

Bisphosphonates are the mainstay of treatment in many adult forms of bone disease. In pediatric bone disease, bisphosphonates are increasingly being used to treat osteogenesis imperfecta, idiopathic juvenile osteoporosis, and fibrous dysplasia [1–6]. Sporadic reports of the use of bisphosphonates in other pediatric conditions, including juvenile chronic arthritis, osteonecrosis, and tibial pseudarthrosis, are also emerging [7–9].

No large randomized trials in pediatrics have been published. Given their extremely long half-life in bone, there is concern both about the safety and appropriateness of bisphosphonate use in children. The report by Whyte et al. [10] of a boy treated with very large doses of pamidronate and diagnosed with the complication of "acquired osteopetrosis" has recently highlighted these concerns. This boy's metaphyseal modeling is clearly abnormal.

The use of bisphosphonates in localized bone disease within an approved protocol is common in our institution. We thus had the opportunity to study metaphyseal modeling on radiographs of children without a systemic bone disease. To do this, we first created a database for boys and girls to establish normal ranges for the modeling leading to the inwasting of the distal femur during growth, relevant to the

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area of abnormal modeling reported by Whyte et al. [10] that was seen after bisphosphonate administration.

Methods

Knee radiographs recorded digitally at our hospital were reviewed. Clinical records had been checked and patients with metabolic disease excluded. A majority of the films were taken for trauma. The protocol was approved by the Institutional Ethics Committee.

We defined modeling at the distal femur by creating a metaphyseal index. This measurement consists of the width of the femur at a defined distance above the growth plate divided by the width of the femur at the growth plate. To remove magnification error, we defined the distance above the growth plate as half the measured width of the growth plate (Fig. 1). The age and metaphyseal index were recorded for the subjects used for the database. For each chronological age year, the mean and standard deviation was calculated for the database group on a Microsoft Excel spreadsheet. The mean value and ±1 and ±2 SD were presented graphically using Excel.

To evaluate the effects of cyclical intravenous bisphosphonate (pamidronate) therapy on distal femoral metaphyseal inwasting in otherwise normal bone, we assessed AP knee radiographs of 20 subjects (11 boys) treated for isolated orthopedic lesions. The diagnoses were osteonecrosis (6), delayed bone healing (4), congenital pseudarthrosis of the tibia (3), bone cyst (3), Perthes disease (2), and miscellaneous (2). The limb examined was that contralateral to any orthopedic lesion. These data were then plotted on the database graph (Fig. 2). The metaphyseal index calculated from the knee radiographs of the subject from the report of "Bisphosphonate-induced osteopetrosis" by Whyte et al. [10], both before and after bisphosphonate therapy, was also plotted on the graph for boys (Fig. 2A).

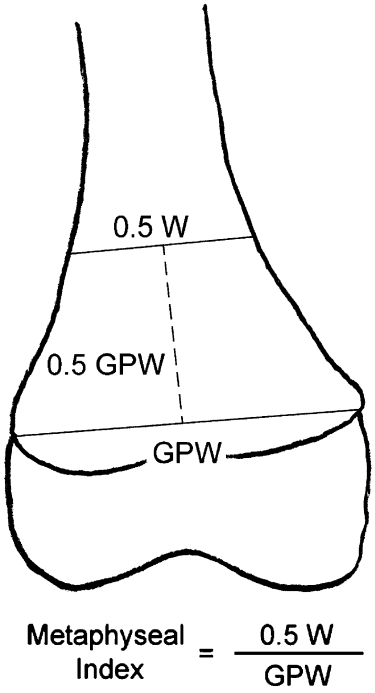

Fig. 1. Method for calculating the metaphyseal index.

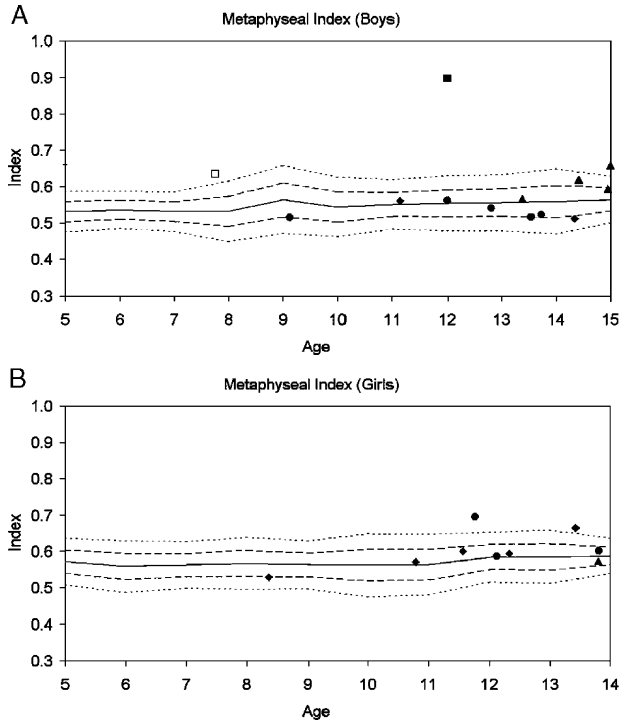

Fig. 2. Graphs of metaphyseal index for distal femur including normative data for boys (A) and girls (B). Mean value = solid line, ±1 SD = dashed line, ±2 SD = dotted line. Subject data: Patient from report of Whyte et al. [10], open square, pre-treatment metaphyseal index; filled square, post-treatment index. Study patients, circle represents total dose <10 mg/kg pamidronate, diamond represents total dose >10 mg/kg pamidronate.

The Z score for each patient, relative to their age, was calculated as

$$Z = \frac{\text{subject value} - \text{mean value}}{\text{standard deviation}}$$

The maximum dose of pamidronate at our institution is 9.0 mg/kg/year; total doses averaged 3.7 mg/kg/year (range 0.8–8.8 mg/kg/year). Modeling occurs over more than 1 year such that the total dose is likely to be an important determinate of any deleterious effects. The mean total dose for the group was 11 mg/kg (range 3–26 mg/kg), given over a mean of 1.35 years.

Results

Metaphyseal index

Informative knee radiographs were available from 468 subjects (Table 1). Metaphyseal index was found to be relatively constant through age. The variability is low, with the coefficient of variation averaging 6% for girls and 7%