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ORIGINAL ARTICLE

The use of intravenous bisphosphonate therapy to treat vertebral fractures due to osteoporosis among boys with Duchenne muscular dystrophy

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Abstract
Summary The impact of intravenous bisphosphonate treatment to treat painful vertebral fractures in boys with DMD has not been documented. In this retrospective observational study of seven boys, 2 years of intravenous bisphosphonate therapy was associated with back pain improvement and stabilization or increases in the height ratios of fractured vertebrae.
Introduction Boys with Duchenne muscular dystrophy (DMD) are at risk for vertebral fractures. We studied the impact of intravenous bisphosphonate therapy for the treatment of painful vertebral fractures in DMD.
Methods This was a retrospective observational study in seven boys with DMD (median 11.6 years, range 8.5 to 14.3) treated with intravenous pamidronate (9 mg/kg/year) or zoledronic acid (0.1 mg/kg/year) for painful vertebral fractures.
Results At baseline, 27 vertebral fractures were evident in the seven boys. After 2 years of bisphosphonate therapy, 17 of the fractures had an increase in the most severely affected vertebral height ratio, 10 vertebrae stabilized, and none showed a decrease in height ratio. Back pain resolved completely (N=3) or improved (N=4). The median change in lumbar spine volumetric bone mineral density Z-score was 0.5 standard deviations (interquartile range, −0.3 to 1.7). Two boys had three incident vertebral fractures in previously normal vertebral bodies that developed over the observation period. There was a decline in the trabecular bone formation rate on trans-iliac bone biopsy but no evidence of osteomalacia. First-dose side effects included fever and malaise (N=4), hypocalcemia (N=2), and vomiting (N=1); there were no side effects with subsequent infusions.
Conclusions Intravenous bisphosphonate therapy was associated with improvements in back pain and stabilization to improvement in vertebral height ratios of previously fractured vertebral bodies. At the same time, such therapy does not appear to completely prevent the development of new vertebral fractures in this context.

Keywords Bisphosphonates · Bone histomorphometry · Bone mineral density · Clinical/pediatrics · Corticosteroid osteoporosis · Vertebral fractures

Abbreviations

BMD	Bone mineral density
CTx	C-telopeptides of type I collagen
DMD	Duchenne muscular dystrophy
GC	Glucocorticoid
IQR	Interquartile range

Introduction

Duchenne muscular dystrophy (DMD) is characterized by progressive muscle weakness and loss of ambulation

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typically by 13 years of age [1]. Although there is no cure for DMD, the advent of glucocorticoid (GC) therapy has improved motor function, resulting in prolongation of independent ambulation [2, 3]. Many patients with DMD have low bone mineral density (BMD), in particular those who receive GC [1, 4], which may result in painful vertebral fractures [5–9].

Bisphosphonates are widely used to treat childhood fragility fractures; however, only one study on bisphosphonate treatment in DMD has been reported to date [10]. In an uncontrolled study of 16 GC-treated boys with DMD, 2 years of daily oral alendronate was associated with stable (i.e., unchanged) spine and total body BMD [10]. On the other hand, intravenous bisphosphonate treatment may be more effective than oral therapy in promoting reshaping of fractured vertebral bodies and thickening of the bone cortex in childhood osteoporosis, phenomena that appear to be unique in children who receive intravenous bisphosphonate therapy during the growth phase [11–16]. The purpose of this study was to report the impact and side effects of intravenous bisphosphonate therapy for the treatment of low-trauma, painful vertebral fractures in boys with DMD.

Patients and methods

This was a retrospective review of bone health outcomes in boys with DMD who were treated for back pain due to vertebral fractures during the course of routine clinical care at the Children's Hospital of Eastern Ontario from 2003 to 2010. The study was approved by the local ethics committee. The diagnosis of DMD was confirmed by genetic testing for mutations in the dystrophin gene or muscle biopsy, in concert with the clinical opinion of a certified pediatric neurologist.

Boys were included in the study if they manifested symptomatic vertebral fractures requiring intravenous bisphosphonate therapy according to the following two criteria: (1) presence of at least one vertebral fracture (T4 to L4) defined according to the Genant methodology [17] as: (a) a prevalent vertebral fracture with a ≥20% loss in the anterior, middle, or posterior height ratio in the absence of a prior radiograph for comparison *or* (b) an incident vertebral fracture with a ≥15% loss in the anterior, middle, or posterior height ratio compared to a prior radiograph and (2) presence of back pain on history that was corroborated by tenderness on palpation over the site of the observed vertebral fracture(s).

Intravenous bisphosphonate treatment regimen

Patients were treated with either intravenous pamidronate (annual dose, 9 mg/kg body weight given as 1mg/kg/day for each of 3 days, every 4 months) or intravenous zoledronic acid (annual dose 0.1 mg/kg body weight, divided into two doses every 6 months). The choice of agent was determined by the local standard of care between 2003 and 2010, and initial treatment to stabilize the osteoporosis was targeted for 2 years.

Clinical data

Height was measured with a Harpenden stadiometer and weight with a digital weight scale. Arm span was used as an estimate of height when measurement of height was not feasible. Height and weight Z-scores were calculated using reference data provided by the National Center for Health Statistics [18]. Pubertal status was evaluated according to the method of Marshall and Tanner [19, 20]. The dose of systemic GC therapy was converted into prednisone equivalents and results were expressed as cumulative GC dose in mg per square meter received during the treatment period [21]. All patients were encouraged to receive the recommended dietary reference intake of calcium and vitamin D for age through diet and/or supplementation [22].

Biochemical measurements

Serum 25-hydroxyvitamin D was measured by radioimmunoassay (Osteo SP; Incstar Corp., Stillwater, MN, USA). Bone-specific alkaline phosphatase was measured by immunoassay (Beckman Coulter, Fullerton, CA, USA). The bone resorption marker, serum C-telopeptide of type I collagen was measured by electrochemiluminescence immunoassay (Elecsys β-CrossLaps Assay Kit, Roche Diagnostics, Laval, Quebec). For the latter two parameters, raw values were converted to age- and sex-specific Z-scores using published reference data [23].

Radiological studies

Radiographs of the left hand and wrist were obtained for evaluation of bone age according to Greulich and Pyle [24]. The films were read by a single pediatric radiologist. A single observer also measured the second metacarpal length, midshaft periosteal diameter, and inner diameter from the bone age hand radiographs [25] to derive the combined cortical width. Measured and derived indices were converted into age- and sex-matched Z-scores according to published reference data [26].

Lumbar spine (vertebrae L2 to L4) and total body areal BMD were measured by dual-energy X-ray absorptiometry in the anterior–posterior direction (Lunar Prodigy; General Electric; Madison, WI, USA). Results were transformed to age- and gender-specific Z-scores using reference data supplied by the manufacturer. To account for bone size, volumetric BMD at the lumbar spine was calculated using the method proposed by Kroger et al. [27] and expressed as the

change during the pre- to post-treatment interval using published reference data [28]. Due to the potential impact of lumbar fractures on the L2 to L4 BMD measurement, boys with fractures in this region were excluded from the group median BMD calculations. The percent change in total body fat mass Z-score was also recorded [28].

Vertebral fracture evaluation

Lateral spine radiographs were performed using standard methods, and the evolution of baseline vertebral fractures following bisphosphonate treatment was documented by carrying out six-point vertebral morphometry from T4 to L4 [29] before and after bisphosphonate treatment. The date of the pre-treatment radiograph was considered baseline, and follow-up radiographs to determine the response to treatment available for analysis were targeted for 2 years later.

From the six-point vertebral morphometry, the anterior, middle, and posterior vertebral height ratios were generated, and the magnitude of the reduction in height ratio was then categorized at baseline and follow-up according to the Genant semi-quantitative classification [17] as follows: grade 0, height ratio loss of 15% or less (normal vertebral body, height ratio 1.0 to 0.85); grade 0.5, height ratio loss of >15–20% (minimal fracture, height ratio 0.84 to 0.80); grade 1, height ratio loss of >20–25% (mild fracture, height ratio 0.79 to 0.75); grade 2, height ratio loss >25–40% (moderate fracture, height ratio 0.74 to 0.60); and grade 3, height ratio loss of >40% (severe fracture, height ratio 0.59 or less).

The change from pre- to post-treatment in the most severely affected height ratio was then calculated. To determine whether a significant change in the height ratio was present, the following analyses were undertaken. First, the measurement errors for anterior, middle, and posterior vertebral height ratios for the 13 vertebra examined in this study (from T4 to L4) were calculated based on a sample of spine radiographs for which six-point vertebral morphometry measurements were repeated by a single operator. The standard deviation of the repeated measurements for each vertebral body and then the root mean square standard deviation for the sample of spine films at each vertebral level were calculated to give the combined within and between standard deviation. The height ratios were compared to the repeatability coefficient based on methods described elsewhere [30, 31]. Changes in height ratios exceeding the repeatability coefficient at the 99% confidence level were considered to be significant. For the 99% confidence level, the repeatability coefficient was obtained by multiplying the combined standard deviation by $\sqrt{2}$ times 2.576. Specifically, increases (i.e., improvements) in vertebral height ratios were considered significant at follow-up if they exceeded the repeatability coefficient limits at the 99% confidence level. A vertebral fracture was deemed to have stabilized if the vertebral height ratio at follow-up compared to baseline was within the repeatability coefficient limits. An existing vertebral fracture was considered to have worsened if the loss in height ratio was ≥15% (i.e., met the definition of an incident vertebral fracture) and exceeded the repeatability coefficient limits. An incident (i.e., new) vertebral fracture in a previously normal vertebral body was defined in the same way as a worsening of an existing fracture.

Trans-iliac histomorphometry

Trans-iliac bone biopsies were performed on three of the boys before and approximately 2 years following initiation of bisphosphonate therapy. Biopsies could not be performed in the remainder of the patients due to hip contractures interfering with the technical aspects of sample procurement. Biopsies were taken at a site 2 cm posterior to the superior anterior iliac spine on days 4 or 5 after dual labeling with demeclocycline (15–20 mg/kg per day taken orally for 2 days, and repeated for 2 more days after a 10-day free interval). Biopsy preparation and histomorphometric analyses were performed as described previously [32]. Measurements were carried out using a digitizing table with OsteoMeasure software (Osteometrics, Inc. Atlanta, GA, USA). Results were compared to the reference data of healthy age- and gender-matched controls established in our laboratory and expressed as percentages of the average value [32].

Statistical analyses

Data are presented as individual patient results, group medians, 25th and 75th percentile interquartile ranges (IQR), and the median change pre- and post-treatment for each clinical parameter. *T* tests were not performed given the limited sample size. Analyses were conducted using SPSS version 19.

Results

Pre-treatment evaluation

Seven boys (median age, 11.6 years; age range 8.5 to 14.3) fulfilled the inclusion criteria and were included in the study (Table 1). Only patient 5 was fully ambulatory pre-treatment; the other boys required wheelchairs (two part time (patients 2 and 4) and four full time). All but patient 3 had received GC therapy (deflazacort, 0.9 mg/kg/day) prior to developing symptomatic vertebral fractures. In this series, none of the boys had a history of extremity fractures prior to treatment.

Table 1 Pre- and post-treatment clinical characteristics of seven boys with DMD treated with intravenous biphosphate therapy for back pain due to vertebral fractures

Clinical parameters at baseline and follow-up	Patient number							
	1	2	3	4	5	6	7	Median (25, 75 IQR)
Demographic and anthropometric characteristics								
Age at DMD diagnosis (years)	7.0	8.3	3.0	4.6	2.9	6.3	5.4	5.4 (3.0, 7.0)
Age pre-treatment (i.e., at baseline, years)	14.3	11.6	14.2	10.2	8.5	11.6	10.4	11.6 (10.2,14.2)
Age at post-treatment (years)	16.2	13.6	16.8	12.2	10.2	13.6	12.8	13.6 (12.2,16.2)
Duration from baseline to post-treatment spine radiograph (years)	1.9	2.0	2.6	2.1	1.7	2.0	2.4	2.0 (1.9, 2.4)
Bone age pre-treatment (years)	12.0	9.5	13.5	9.5	NA	9.0	9.0	9.5 (9.0,12.4)
Bone age change (years)	4.0	1.5	3.5	3.0	NA	0.5	3.0	3.0 (1.3, 3.6)
Pubertal stage pre-treatment (Tanner)	1	1	3	1	1	1	1	
Pubertal stage post-treatment (Tanner)	4	1	4	1	1	2	2	
Height Z-score pre-treatment	−4.2	−2.5	−1.4	−0.5	−1.9	−1.7	−1.1	−1.7 (−2.5, −1.1)
Height Z-score change	0.9	−1.1	−1.4	−1.1	−0.7	−0.8	0.1	−0.8 (−1.1, 0.1)
Weight Z-score pre-treatment	−2.3	−1.4	0.4	1.8	−1.0	0.7	1.8	0.4 (−1.4, 1.8)
Weight Z-score change	−0.3	−0.2	−2.2	−0.3	−1.3	−0.3	0.7	−0.3 (−1.3, −0.2)
Glucocorticoid treatment[a]								
Duration of GC therapy pre-bisphosphonate treatment (days)	2,321	796	0	673	1,127	1,288	1,249	1,188[b] (765, 1,546)
Cumulative GC dose pre-bisphosphonate treatment (mg/m^2)	23,527	11,464	0	7,700	19,352	8,285	26,248	15,408[b] (8,138, 24,207)
Cumulative GC dose during bisphosphonate treatment (mg/m^2)	0	9,838	0	7,901	12,553	7,268	8,149	8,149[b] (7,584, 11,195)
Skeletal characteristics								
Bisphosphonate agent	Pam	Pam	ZA	ZA	ZA	ZA	ZA	
LS areal BMD Z-score pre-treatment	−4.9	−2.1	−2.3	−0.4	−2.3	−0.5	−2.0	−2.1 (−2.3, −0.5)[c]
LS areal BMD Z-score change	3.9	0.0	−0.3	0.3	1.7	−0.1	2.4	0.0 (−0.2, 1.0)[c]
LS volumetric BMD Z-score change	4.2	0.1	−0.7	0.5	2.5	0.9	4.2	0.5 (−0.3, 1.7)[c]
Second metacarpal cortical width Z-score pre-treatment	−3.1	−2.0	−1.2	−0.1	NA	−0.3	−0.2	−0.7 (−2.3, −0.2)
Second metacarpal cortical width Z-score change	0.1	0.2	0.1	−1.4	NA	−0.9	0.9	0.1 (−1.0, 0.4)
25-hydroxyvitamin D level pre-treatment (nmol/L)	63	65	50	49	43	61	37	50 (43, 63)
25-hydroxyvitamin D level change (nmol/L)	−2	27	35	10	92	9	17	17 (9, 35)
Serum C-Telopeptide Z-score pre-treatment	−1.6	−2.2	−0.8	−3.1	−1.5	NA	−1.6	−1.6 (−2.4, −1.3)
Serum C-Telopeptide Z-score change	NA	0.0	−2.6	0.7	0.1	NA	−1.2	0.0 (−1.9, 0.4)
Bone-specific alkaline phosphatase Z-score pre-treatment	NA	−0.9	−0.1	−0.7	−0.6	−0.7	−0.5	−0.6 (−0.8, −0.4)
Bone-specific alkaline phosphatase Z-score change	NA	0.6	−1.0	−0.4	0.0	NA	−0.2	−0.2 (−0.7, 0.3)
Number of vertebral fractures in each severity category pre-treatment								Total, *n*
Minimal	0	2	0	0	1	1	1	5
Mild	2	1	0	0	0	0	1	4
Moderate	5	0	1	4	0	0	4	14
Severe	2	0	0	0	0	0	2	4
Number of vertebral fractures in each severity category post-treatment								
Normal	8	1	1	3	0	1	5	19
Minimal	0	0	0	1	0	0	2	3
Mild	0	1	0	0	1	0	0	2
Moderate	1	1	0	0	0	0	1	3
Number of incident vertebral fractures identified during the 2-year treatment period	0	2	0	0	1	0	0	3

NA not available, *Pam* pamidronate, *ZA* zoledronic acid, *aBMD* areal BMD, *GC* glucocorticoid

[a] Cumulative glucocorticoid dose is reported in prednisone equivalents

[b] Median excludes patients not taking glucocorticoids

[c] Median excludes patients 1 and 7 with lumbar spine vertebral fractures

Baseline radiographs revealed a total of 27 fractured vertebrae in the seven boys (Fig. 1). The median time from GC initiation to presentation with the first vertebral fracture was 2.1 years (minimum, 0.2 years; maximum, 5.4 years). Note that four of the boys had vertebral fractures detected on annual spine radiograph as part of bone health monitoring whereas three boys presented with painful vertebral fractures in the absence of spine health surveillance. The seventh thoracic vertebra was the most frequent site of fracture. At baseline, three patients had one vertebral fracture, two boys manifested two to four fractures, and two boys had more than five vertebral fractures. Fracture severity according to the boys' worst fracture grade was as follows: two boys had grade 0.5 vertebral fractures, one boy had grade 1, two boys had grade 2, and two boys had grade 3 vertebral fractures. Eighteen percent (5/27) of the vertebral fractures were minimal (grade 0.5), 15% were mild (4/27), 52% (14/27) were moderate, and 15% (4/27) were severe. Twenty (74%) of the vertebral fractures had anterior wedge morphology, and seven (26%) were biconcave.

Post-treatment results

Clinical data

The clinical profiles of the boys 2 years post-treatment compared to baseline including anthropometry, steroid therapy, and skeletal characteristics are described in Table 1. Changes in ambulatory status were as follows: patient 5 remained fully ambulatory and patients 2 and 4 became completely wheelchair-bound during the treatment period. The median change in total body percent fat Z-score was 0 (IQR, −0.3, 0.5). Patient 1 discontinued GC therapy 4 months prior to bisphosphonate initiation; patient 3 had no history of GC therapy. The other patients remained on GC during the bisphosphonate treatment period. Patient 3 also developed critical cardiac failure that was associated with significant weight loss (weight Z-score declined 2.2 SD over 2.6 years).

Extremity and vertebral fractures

Patient 6 sustained a low-trauma tibia fracture during bisphosphonate therapy; none of the other boys had radiologically confirmed extremity fractures. Figure 2a shows the change in the most severely affected height ratio between baseline and follow-up for each fractured vertebral body per child. All of the vertebral height ratios either stabilized or improved. The most striking change was that all four of the severe vertebral fractures showed improvement at follow-up (i.e., all vertebral height ratios completely normalized). Increased density and reshaping of the vertebral bodies is shown in patient 1, Fig. 2b.

In two boys, there were three incident vertebral fractures in previously normal vertebral bodies. For patient 5 at T7, there was progression from 2% to 19% loss in anterior height ratio (representing a minimal fracture). Patient 2 had the other two incident fractures—a moderate (grade 2) fracture at T8 (a 7%

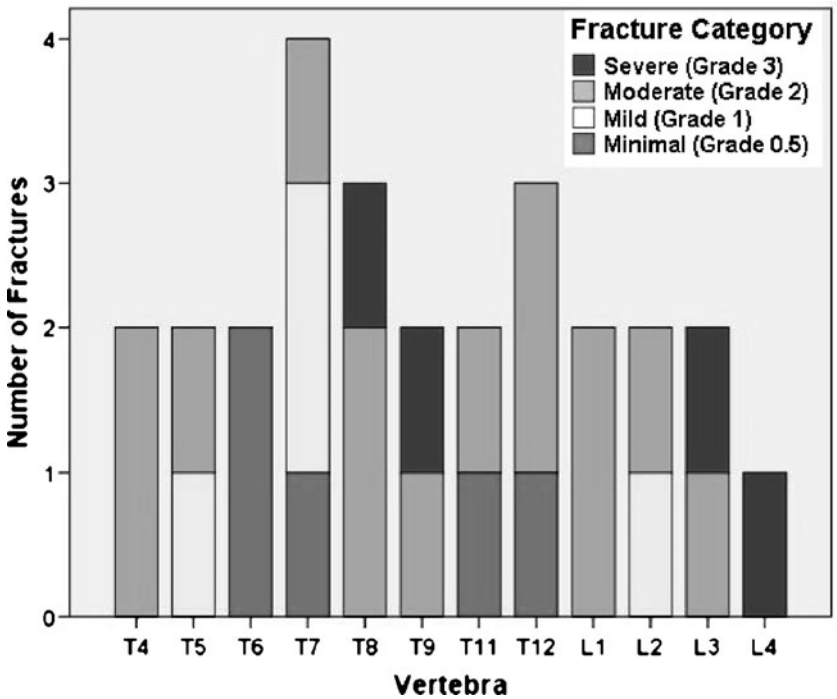

Fig. 1 Frequency and location of vertebral fractures in boys with DMD pre-bisphosphonate treatment in relation to the number of fractures identified as minimal (grade 0.5), mild (grade 1), moderate (grade 2), and severe (grade 3) at each vertebral level

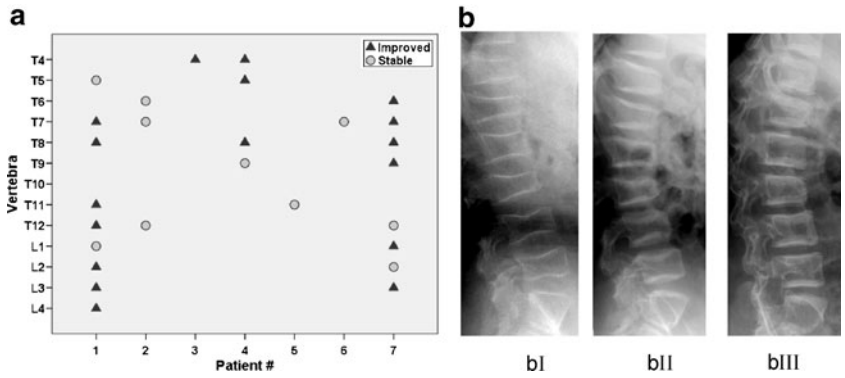

Fig. 2 **a** Change in the most severely affected height ratio after 24 months of IV bisphosphonate therapy for the seven boys with DMD. All vertebral fractures diagnosed at baseline either stabilized or improved. **b** Vertebral fractures before (*bI*) and after pamidronate treatment (12 months *bII* and 24 months *bIII*) in a 15-year-old boy with DMD (patient 1). Note the reshaping of the vertebral bodies following treatment, as well as the overall increase in the density of the vertebral endplates

to 36% loss in anterior height ratio) and a mild (grade 1) fracture at L1 (a 2% to 21% loss in anterior height ratio).

Back pain, bone densitometry, second metacarpal morphometry, and bone biochemistry

At follow-up, three boys reported complete back pain resolution and the remaining reported significant improvement. Back pain improved in all patients within 30 days of bisphosphonate therapy administration. The two boys who developed incident fractures during treatment did not report back pain. All boys except patient 3 experienced increases in spine volumetric BMD post-infusion; this patient presented with cardiac failure and significant weight loss during this time. Cortical width at the second metacarpal increased minimally in three boys, by a clinically significant magnitude in one, and declined in three.

Bone histomorphometry

The results of trans-iliac histomorphometry are presented in Table 2, before and after 2 years of intravenous bisphosphonate therapy in three boys. The cortical width increased in patient 1; this boy was unique in that he had discontinued GC therapy 4 months prior to initiation of bisphosphonate therapy and was the only patient to manifest an increase in height Z-score (Table 1). In patient 2, a decline in trans-iliac cortical width was evident—this boy had stable doses of GC therapy throughout the bisphosphonate treatment interval. Patient 3 also experienced a decline in cortical width despite being steroid-naïve both pre- and during bisphosphonate treatment; he was the only patient to have developed cardiac failure during the treatment period. There was a fall in trabecular bone volume in patients 1 and 2 with little change in patient 3. The trabecular bone formation rate in the two patients for whom the parameter was available also declined, as expected with bisphosphonate therapy. Despite the decline in bone turnover in all three boys with prolongation of the mineralization lag time, there was no evidence of an accumulation of osteoid (osteomalacia).

Side effects

Four of the seven boys manifested one or more clinical side effects after the first infusion including fever (n=4) and asymptomatic ionized hypocalcemia developed in two boys when measured 48–72 h post-infusion. One boy (patient 3) suffered nausea and vomiting and was unable to eat well or ingest calcium supplementation for 5 days; he developed symptomatic hypocalcemia (paresthesiae) requiring intravenous calcium therapy. He was further treated with ondansetron, which was effective in eliminating his gastrointestinal symptoms and allowing him to resume normal intake of food and calcium supplementation. These symptoms did not recur with subsequent infusions.

Discussion

In this study, we have shown that intravenous bisphosphonate treatment used to treat symptomatic vertebral fractures among boys with DMD was associated with improvement in back pain in all patients. We also observed stabilization to improvement in the height ratios of the previously fractured vertebral bodies as well as increases in lumbar spine volumetric BMD (the latter, in all but one patient). One boy, patient 3, developed cardiac failure during the treatment period that was associated with a clinically significant decline in weight Z-score. The boy's changes in weight may have impacted the BMD results since increases in abdominal mass are associated with false elevations in DXA-based BMD and conversely, dramatic weight loss can lead to the impression of BMD Z-score decline. In the setting of an

Table 2 Changes in trans-iliac histomorphometry after 2 years of intravenous biphosphate therapy in boys with bone fragility and DMD

Biopsy parameters at baseline and follow-up	Patient number[a]		
	1	2	3
Age at pre-biopsy	13.8	11.6	14.2
Age at post-biopsy	16.2	13.9	16.9
Duration between pre- and post-treatment biopsies	2.5	2.3	2.8
Core width (% of healthy mean) pre-treatment	70	99	77
Core width % change pre- to post-treatment	−35	46	−31
Cortical width (% of healthy mean) pre-treatment	32	33	46
Cortical width % change pre- to post-treatment	221	−41	−23
Bone volume per tissue volume (% of healthy mean) pre-treatment	31	45	32
Bone volume per tissue volume % change pre- to post-treatment	−44	−34	0.3
Bone formation rate (% of healthy mean) pre-treatment	56	51	108
Bone formation rate % change pre- to post-treatment	NA	−80	−94
Osteoid thickness (% of healthy mean) pre-treatment	52	52	71
Osteoid thickness % change pre- to post-treatment	−21	−16	7
Mineralization lag time (% of healthy mean) pre-treatment	55	65	67
Mineralization lag time % change pre- to post-treatment	NA	444	638

NA not available

[a]All patients were actively receiving cyclical, intravenous bisphosphonate therapy at the time of bone biopsy

uncontrolled study, we cannot definitively conclude that the improved back pain was directly attributable to the intravenous bisphosphonate therapy. However, the fact that vertebral height ratios in vertebral bodies that were fractured at baseline stabilized or improved in all patients, and lumbar spine BMD improved in all but one suggests a positive impact of the therapy. Overall, the median increase in spine volumetric BMD Z-score was half a standard deviation, compared to the lack of response to oral alendronate in the Hawker et al. report [10]. These observations are particularly notable in the context of ongoing, potent threats to bone health including the progressive myopathy plus continuous GC therapy in 5 of 7 patients. The impact of intravenous bisphosphonates on bone pain is well known, having been described in children with osteogenesis imperfecta [11] and fibrous dysplasia [33].

In children with osteogenesis imperfecta, it has been shown that the main effect of bisphosphonate therapy that confers bone strength is an increase in cortical width at various skeletal sites [34, 35]. This is a growth-dependent process that occurs in bones undergoing modeling (the process by which bones undergo changes in geometry). In our report, it is not surprising that the only patient to show an increase in the width of the cortices at the second metacarpal and the iliac crest was the patient who showed improvement in growth velocity. This patient (patient 1) stopped GC treatment prior to bisphosphonate initiation and went on to evolve through puberty and increase height Z-score significantly. The results in patient 1 highlight an important concept in pediatric osteoporosis management; despite low bone turnover on trabecular surfaces even before initiating bisphosphonate therapy (with further declines in bone turnover documented on iliac biopsy as expected with bisphosphonate therapy), improved cortical width and reshaping of vertebral bodies were possible in the presence of normal linear growth.

Our findings also highlight that the BMD criteria recommended by the International Society for Clinical Densitometry [36] for the diagnosis of pediatric osteoporosis may not apply to all children. Specifically, these criteria state that areal BMD Z-scores below −2.0 must be present, along with a clinically significant fracture history, to diagnose a child with osteoporosis. Our study shows that lumbar spine areal BMD Z-scores can be better than −2.0 despite a clinically significant vertebral fracture history in high risk children.

In this report, we chose a 15% reduction in height ratio to define an incident vertebral fracture, a cutoff which is supported by a recent publication by Gaca et al. [37] who found that 95% of healthy children had an anterior to posterior vertebral body height ratio greater than 0.89 (i.e., no more than an 11% reduction) from T10 to L3 based on sagittal reformations of vertebral bodies on abdominal and pelvic computed tomography scans. These authors suggested that an anterior to posterior height ratio less than 0.89 should raise the possibility of a vertebral injury. Therefore, the ratio cut-off of 0.85 when a prior film is available for comparison appears reasonable for defining a vertebral fracture, particularly since the loss in height ratio in this study was associated with localized back pain on palpation and persistence of risk factors for bone fragility (GC use and myopathy).

The fact that two boys, both of whom continued to receive GC therapy during the treatment period, developed incident vertebral fractures on intravenous bisphosphonate treatment highlights that the deleterious effect of high-dose

GC therapy may not be completely over-ridden by anti-resorptive agents. This observation opens the door for consideration of anabolic drugs in the treatment of DMD-related osteoporosis, particularly since bone formation was low on trabecular surfaces pre-treatment in this case series (80–90% reduction on iliac biopsy). Low bone formation is a typical finding in chronic disuse and GC-induced osteoporosis [38]. Whether similar efficacy with less reduction in bone turnover can be achieved with lower dose intravenous bisphosphonate therapy remains untested [39], suggesting the need for head-to-head trials with varying doses.

Overall, the therapy was generally well tolerated. The symptoms described in our study are in keeping with the classic "first phase reaction" described in numerous other reports of intravenous bisphosphonate therapy in children [11, 40]. The patient who developed symptomatic hypocalcemia attributed to inanition resulting from vomiting has prompted our center to aggressively treat these gastrointestinal symptoms with an anti-nausea agent when first reported. This patient had received zoledronic acid, which may be associated with more frequent vomiting compared to intravenous pamidronate [41].

Large prospective studies are needed to determine the incidence of osteoporosis in pediatric DMD and the natural history of vertebral fractures in this context. King et al. [7] have shown that the prevalence of symptomatic vertebral fractures in boys with DMD is 30%; however, studies suggest that children with vertebral fractures due to chronic illness are frequently asymptomatic and thereby go unrecognized [42–44], a phenomenon that merits understanding in boys with DMD. To date, DMD vertebral fracture studies have been limited to cross-sectional study design [7] or retrospective reports [6]; there are no prospective, longitudinal studies available that have described the evolution of vertebral fractures over time. As such, whether boys with DMD can undergo spontaneous reshaping of vertebral bodies to restore normal vertebral dimensions remains unknown. Among children with transient threats to bone health such as inflammatory disorders or leukemia, vertebral body reshaping through bone growth has been reported [45, 46]. Given the persistence of risk factors for bone fragility in boys with DMD (myopathy and often long-term glucocorticoid therapy), the potential for spontaneous vertebral body reshaping may be minimal or absent. This hypothesis requires verification through prospective observational studies.

What does this mean in practical terms for the timing of bisphosphonate initiation in pediatric DMD? We have shown the benefits of such therapy when given intravenously for symptomatic vertebral fractures. This provides a reasonable indication for therapy until there is published evidence about the benefits and risks of initiating therapy prior to the onset of osteoporosis-related symptomatology. At the same time, studies are needed to define the optimal bisphosphonate drug and dosing regimen in this context, given the varied, published protocols for bone fragility treatments that have not yet been formally tested for relative efficacy in this or other populations [11, 39, 47]. Such studies are particularly justifiable in DMD given the recent evidence that bisphosphonate use in combination with steroids appears to prolong life expectancy in these boys [48].

In conclusion, this report supports the use of intravenous bisphosphonate therapy on compassionate grounds for boys with DMD and symptomatic vertebral fractures. Our novel data provide a rationale to document the timing and incidence of vertebral fractures in steroid-treated DMD in a large cohort of patients and therefore inform the design of much needed trials to prevent bone fragility in this high risk setting.

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