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Case Report

Bone Shock Absorption in Pediatric Patients With Osteogenesis Imperfecta – A Pilot Study to Assess the Potential of this Technique to Detect Differences in Bone Fragility

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Introduction

Inadequate bone mass acquisition during childhood is associated with an increased lifetime risk for fractures. Currently, dual energy x-ray absorptiometry (DXA) is used clinically to measure areal bone mineral density (aBMD) but is not sensitive enough to quantify risk of fragility fractures in children (*1*).

Osteogenesis imperfecta (OI) is most commonly due to mutations in collagen (*COL1A1 or COL1A2*) that impairs triple helix formation, resulting in decreased bone mineralization. OI type 1 is the mildest form, generally present during childhood with recurrent fragility fractures. Treatment with bisphosphonate therapy has been shown to increase aBMD and reduce fractures, but is generally reserved for those suffering multiple fractures per year (*2*). Clinical decision making on bisphosphonate use is often based on aBMD *Z* score (*2*). Despite improvements in aBMD, fracture rates remain elevated indicating that there are other factors to consider in assessing skeletal integrity of children with primary forms of osteoporosis.

Bone Shock Absorption (BSA) is a technique that measures damping, the ability of bone to absorb external forces, dynamically (*3*). Higher damping indicates an increased resistance to fracture. BSA has been validated in postmenopausal women diagnosed with osteoporosis (by DXA), differentiating those with and without fractures. BSA has not previously been tested in young children but offers an alternative, noninvasive method to assess the skeletal integrity of children with bone disease. Here we report the use of the BSA technique in prepubertal children to gather preliminary data on its ability to discriminate the degree of bone fragility in those with OI compared to healthy children of similar age, sex, and race.

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Patients and Methods

Participants

Children ages 5–18 years with genetically confirmed OI Type 1 were eligible for participation in this pilot study. Patients with OI were ineligible for participation if they had another neurological disorder, were unable to stand or walk for 10 min without discomfort or assistance, or had indwelling metal hardware. Three prepubertal children were enrolled, with Cases 1 and 2 being siblings. Pertinent demographics and bone history are described in Table 1. For Case 1, bisphosphonate infusions were discontinued because of improvement in lumbar spine aBMD *Z* score to −1.1 but were subsequently resumed due to ongoing vertebral compression fractures. For Case 2, bisphosphonate infusions were discontinued. For Case 3, bisphosphonate infusions have not been used.

Six healthy children of similar age and race to cases were included as controls. To participate, these control subjects also had to satisfy the same exclusion criteria as cases but also have no family history of bone disease.

Table 1
Relevant Bone Data for Case Subjects

	Historical data			Current data at time of BSA	
	Age/race/sex	Fracture history	Bisphosphonate history	Height/weight	BMD *Z* score[a]
Case 1	9y10m Caucasian M	Left tibia *(age 18m)* Right tibia *(age 18m)* Right tibia *(age 2y8m)* T7 *(age 7y6m)* T9-T11 *(age 9y3m)*	Pamidronate monthly (2y8m – 3y8m) Zoledronic Acid every 6 months (9y7m – current)	135.7 cm (48%) 45.9 kg (97%)	−3.3 *(6)*
Case 2	7y11m Caucasian F	Right tibia *(age 7m)* Left tibia *(age 11m)* Left Ulna *(age 2y10m)*	Pamidronate monthly (1y3m – 2y6m)	122.2 cm (16%) 27.7 kg (6%)	+0.5
Case 3	7y7m Caucasian F	Left radius/ulna *(age 4y8m)* Right radius *(age 4y10m)* Left *radius (age 6y3m)*	Not applicable	119.8 cm (16%) 28.7 kg (78%)	−0.9

[a]Lumbar spine height adjusted *Z* score for aBMD (*4*).

None of the controls had ever sustained a fracture except Case 8 (traumatic distal forearm fracture at 4y10m).

DXA

Subjects underwent DXA scans (Hologic) of the anterior-posterior lumbar spine. Height adjusted *Z* scores were calculated using BMDCS reference data *(4,5)*.

BSA Testing

For each subject, low-mass accelerometers were attached at the lateral femoral condyle and tibial tuberosity to capture damping and resonance frequencies while minimizing the effect of soft tissue according to the technique previously described *(6)*. Subjects tapped 1 heel on the force platform (Model OR6-7-1000, Advanced Mechanical Technology Inc. Watertown, MA) with a force used during normal walking at least 5 times for an average damping value. Accelerometers measure resonance frequency as force propagates up through the body and provides a frequency response function. Custom software was used to analyze frequency response functions and select crucial peaks to calculate damping.

Statistical Analysis

Due to sample size, nonparametric statistics were used for analysis. Specifically, Wilcoxon rank sum test was used to examine differences between OI and control subjects, using the mean of the repeated trials. A general linear model was used in order to incorporate repeated trials within subject to estimate the least-square mean and associated standard error for the figures.

Results

Statistical analysis indicated a significant difference between cases and controls at the right lateral femoral condyle ($p = 0.04$). This trend seemed to be more evident in males than females (Fig. 1).

The 2 girls with OI were compared separately, as Case 2 received bisphosphonate therapy whereas Case 3 had not. Case 2 currently has a higher aBMD *Z* score than Case 3, but damping values are lower (Fig. 2).

For all subjects, no relationship was found between DXA aBMD *Z* scores and damping measured by BSA (Fig. 3).

Fig. 4 compares damping values reported here to available adolescent and adult data *(8,9)*.

Discussion

DXA is an important tool for guiding the clinical diagnosis and management of osteoporosis in adults and children. However, there are limitations in its ability to fully assess bone fragility and the response of bone to mechanical loading. In children specifically, the ability of DXA to predict future fracture risk is limited. Pediatricians have few tools to assess response to bisphosphonate therapy in children with disorders of bone metabolism receiving this intervention, as bone turnover markers are not routinely available for clinical use. Thus, additional measures to assess bone strength are greatly needed.

BSA has been proposed as an additional tool to predict fracture risk in adult women with osteoporosis (*6*). This pilot study demonstrates the practicality of BSA in prepubertal children. Based on previous populations tested (*3,7*), the damping values obtained in this age group appear to be valid. Fig. 4 suggests a pattern of damping values declining with age, which may be due to

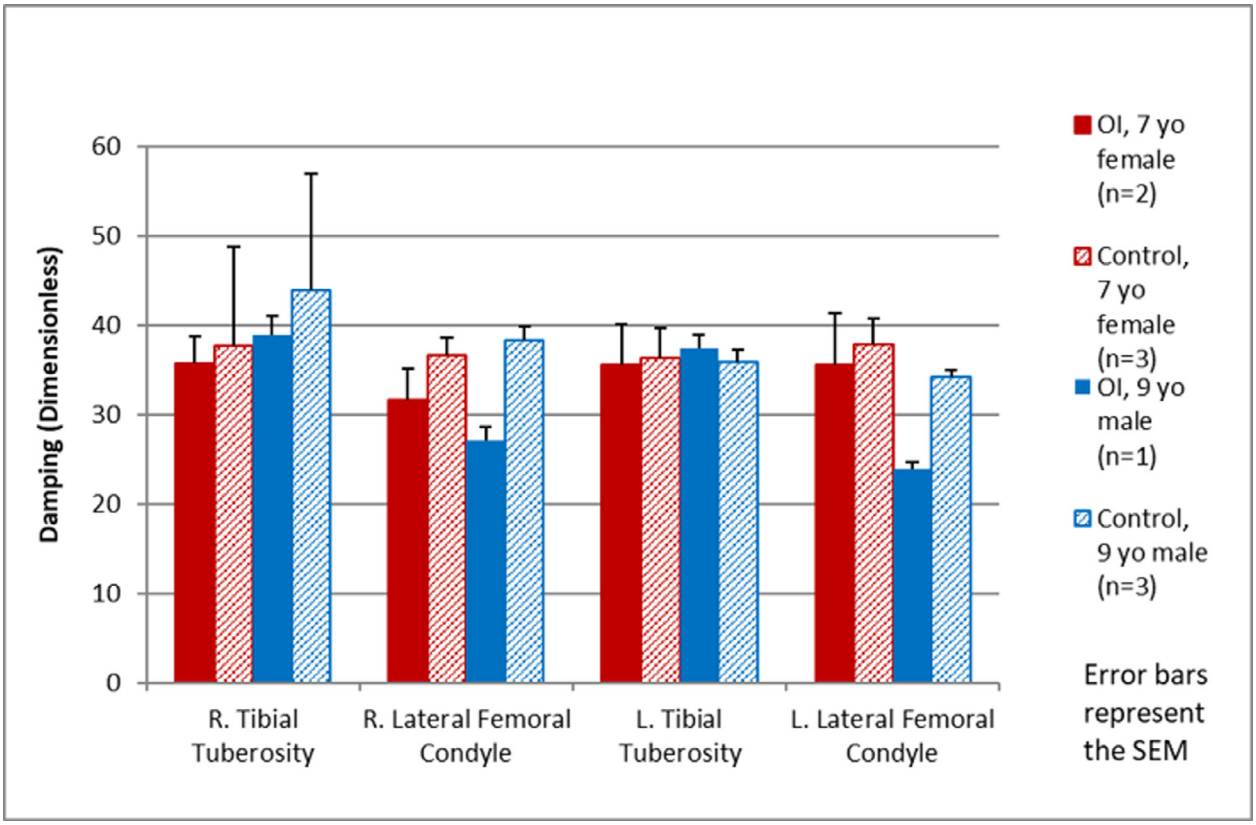

Fig. 1. Comparison of group mean damping value by anatomical site.

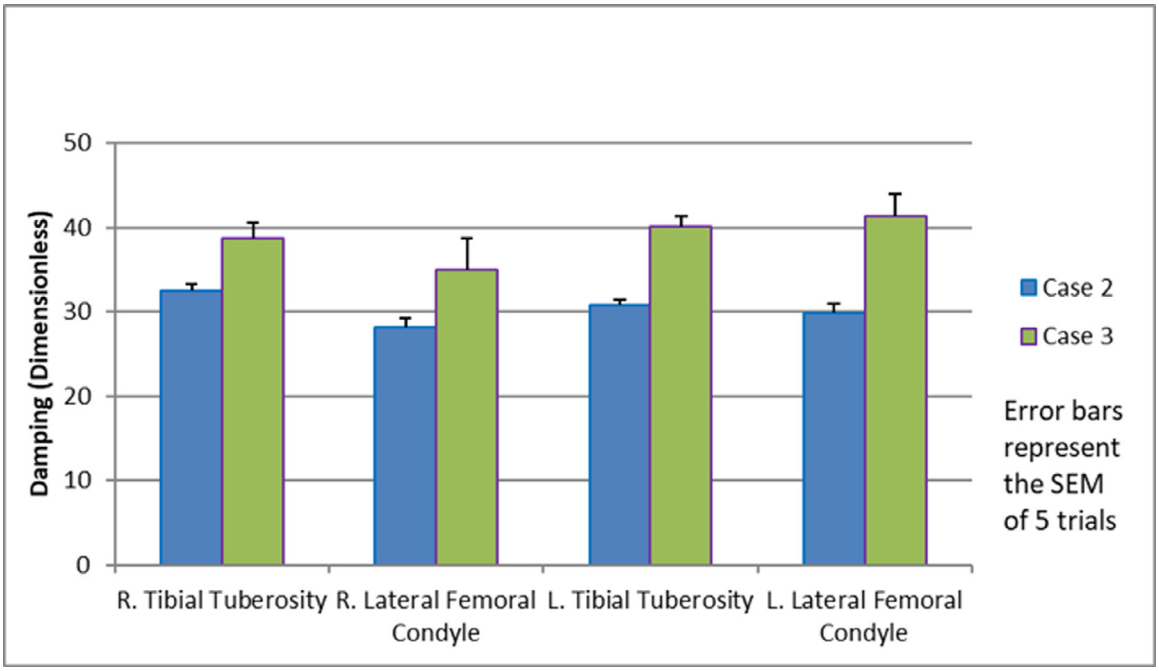

Fig. 2. Comparison of damping values between two case subjects; Case 2 receives bisphosphonate treatment, Case 3 does not.

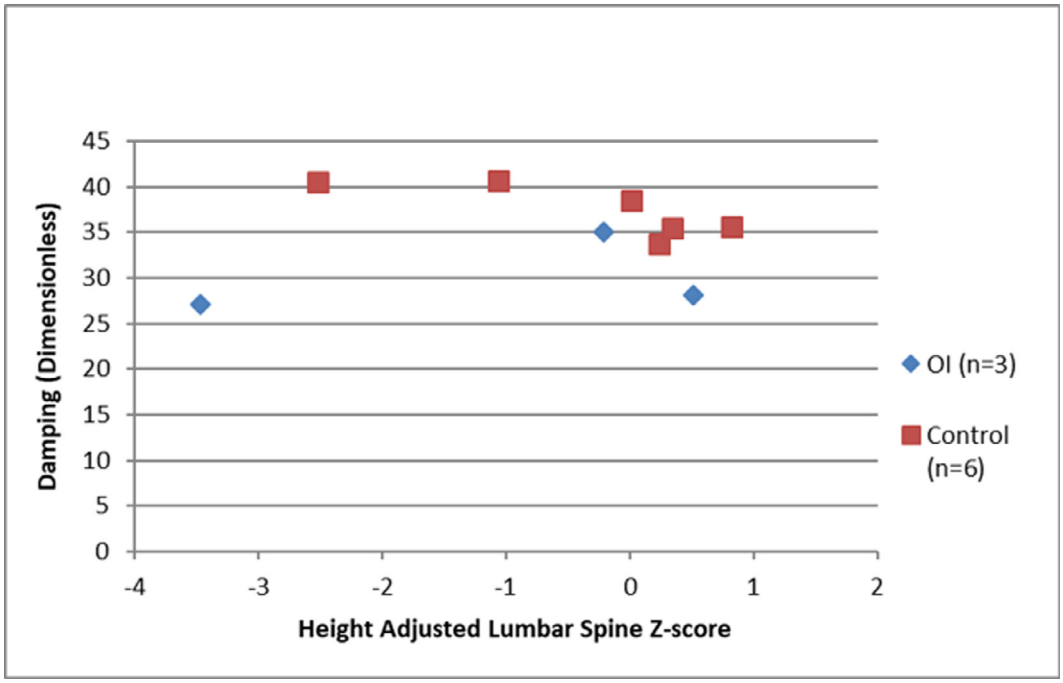

Fig. 3. Height adjusted lumbar spine *Z* score vs within subject mean right lateral femoral condyle damping.

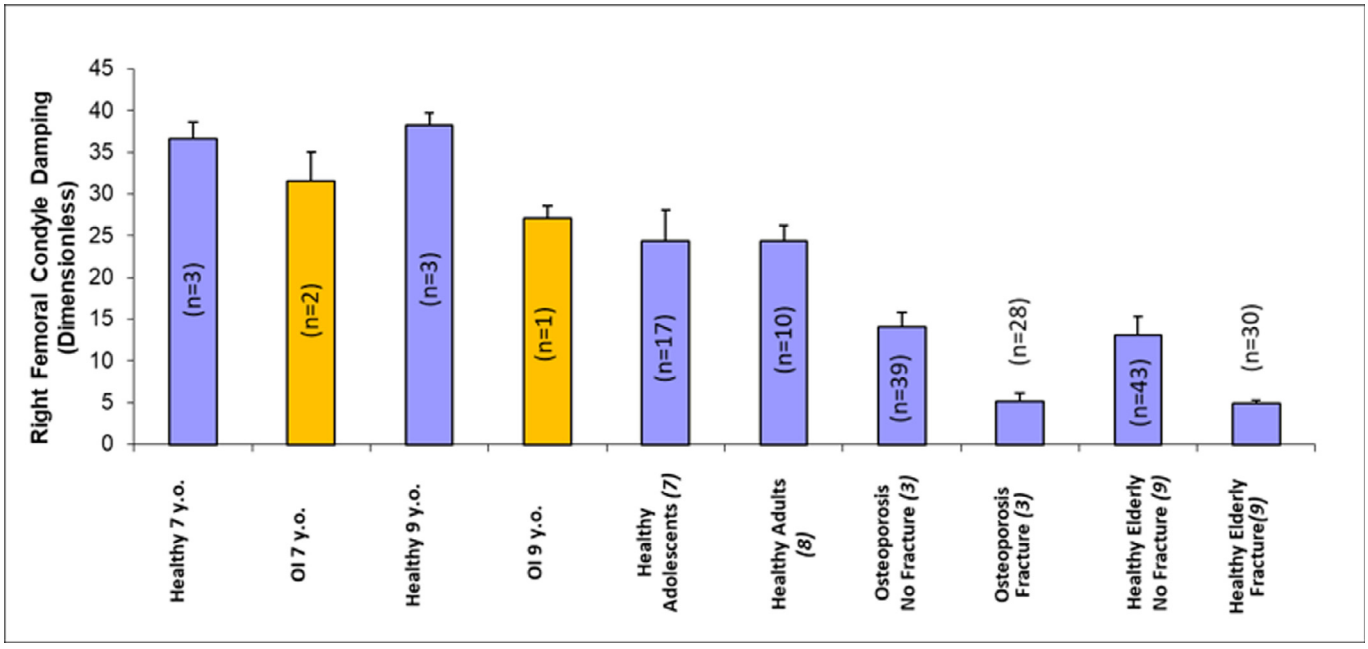

Fig. 4. Age and disease related changes in damping; osteogenesis imperfecta (OI) Type I diagnosed genetically, osteoporosis diagnosed by DXA.

differences in collagen to mineral ratios. The difference in ability to discriminate between the left and right leg may be due to handedness, as not all subjects were right-handed.

Results of our study are limited, given its small sample size, however the cases studied were representative of typical children with OI Type 1. We found no relationship between aBMD *Z* scores and damping, suggesting

that BSA may provide additional unique information about bone health. As trabecular microarchitecture is critical in shock absorption, the lumbar spine scan site, a region of primarily trabecular bone, is ideal for comparison with damping. Trabecular bone is also present at metaphyses of long bones. Measurements of density and microarchitecture at these regions may show different correlations with damping, providing a more complete picture of bone integrity. A larger study in prepubertal, healthy children is necessary to clarify our findings and determine the pattern of normal damping throughout childhood, creating a reference for future investigation.

Our data suggests that BSA may detect differences in children with genetic conditions of skeletal fragility, similar to findings in postmenopausal women (*3*). Bisphosphonate therapy normalized aBMD *Z* score (Case 2), however damping was lower compared to Case 3 with a similar aBMD though no history of bisphosphonate exposure. This suggests that differences in bone integrity remain despite normal density. The small sample size in this study precludes the ability to detect statistically significant differences in damping and fracture rates between cases and controls and within bisphosphonate treated and untreated cases. Further research into BSA and other measures of bone's ability to resist fracture would improve clinical treatment decisions, especially for children with clinically significant fragility fractures.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jocd.2019.09.004.

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