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The use of bone age for evaluating bone density in patients with Duchenne muscular dystrophy: a preliminary report

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Abstract

Introduction: Patients with Duchenne muscular dystrophy (DMD) exhibit low bone mineral density and increased fracture risk. Because glucocorticoid therapy results in delayed puberty and short stature, it is important to account for delayed skeletal development when interpreting their bone mineral density.

Methods: 12 glucocorticoid-treated patients with DMD were evaluated by dual x-ray absorptiometry (DXA) scans and wrist x-rays to estimate bone density and bone age, respectively. Z-scores were determined based on chronological age. Each patient was assigned a “corrected” birth date calculated based on bone age and a bone-age-corrected z-score determined.

Results: Z-scores adjusted for chronological age were lower than those adjusted for bone age.

Discussion: We suggest the use of bone age as an alternative to chronological age for the analysis of bone mineral density in glucocorticoid treated-patients with DMD. Additional research is needed to determine the optimal method to predict fracture risk in this patient group.

Keywords

Duchenne muscular dystrophy; osteoporosis; bone mineral density; DXA; glucocorticoid

1. Introduction

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy in childhood, affecting 1.12 in 10,000 males aged 5 to 24 years in the United States.¹

Glucocorticoids have been and remain the mainstay of therapy to slow the decline of

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cardiopulmonary function and muscle strength,² thus delaying loss of ambulation³ and lengthening life expectancy.⁴

As a result of glucocorticoid therapy, patients with DMD often exhibit low height for age and delayed puberty, resulting in delayed skeletal maturity and increased bone fragility.⁵ This translates into an increased risk of compression fractures of the spine and long bone fractures, often heralding the loss of mobility.^{5,6} Thus, the timely diagnosis and treatment of osteoporosis in these patients is one of the main goals of disease management.

Recent DMD care considerations have replaced bone mineral density measurement with serial spine radiographs as the primary tool for monitoring and diagnosing osteoporosis, which is now based on the evidence of bone fragility such as vertebral fractures and changes in spine morphology. However, bone mineral density still plays a role in monitoring the trajectory of bone health, whether or not the patient has developed clinically significant bone fragility. This shift away from bone mineral density measurement for the diagnosis of osteoporosis is based on the failure of dual x-ray absorptiometry (DXA)-based z-scores to accurately predict fractures, as well as a wide variability in z-scores depending on the reference population used.^{7,8}

Most studies regarding bone mineral density in patients with DMD have used age-matched controls as the reference population for calculation of z-scores. However, since delayed skeletal maturity and short stature lead to smaller bone size, the use of age-matched normal controls often leads to an overestimation of mineral deficit.⁶ Studies have demonstrated this by comparing bone mineral density values obtained by adjustment for height versus age matched controls. Adjustment of bone mineral density for height in patients with DMD demonstrated an attenuated degree of deficit when compared to adjustment for chronological age.⁹ Similarly, although the adjustment of bone mineral density for chronological age in patients with DMD demonstrated lower bone mineral density, there was no difference when bone mineral density was adjusted for height for age (the age at which 50% of children reach the patient's height).¹⁰

Although adjustment for height may be a useful method for more accurate estimation of bone mineral density in patients with DMD, height measurement is difficult to obtain once patients with DMD develop contractures and lose the ability to stand. Bone age, an alternate indicator of delayed skeletal maturity, can be obtained relatively simply by wrist x-ray. We propose the use of bone age rather than chronological age for the adjustment of bone mineral density of glucocorticoid-treated patients with DMD. Since these patients usually have delayed skeletal maturity, we hypothesize that this adjustment will result in higher z-scores compared to adjusting for chronological age.

2. Subjects and Methods

A. Patients:

This retrospective chart review reports data from 12 patients with DMD followed at the University of Iowa Hospitals and Clinics, Muscular Dystrophy Clinic. All patients for whom concurrent DXA (to estimate bone mineral density) and wrist x-ray (to estimate bone age)

were available in the medical record were included. The diagnosis of DMD in these patients was established on the basis of genetic testing and clinical course consistent with the diagnosis. This study was approved by the Institutional Review Board at the University of Iowa.

B. Data Elements:

Key data elements were patient demographics, Body Mass Index (BMI), glucocorticoid use, antiresorptive drug use, wheelchair use, total testosterone level at the time of DXA scan, areal bone mineral density by DXA and bone age estimates based on wrist x-rays. Bone age was estimated using the Greulich & Pyle method, which is based on the comparison of maturity indicators in patients' hand-wrist images with reference images representing different stages of skeletal maturation.¹¹ DXA scans were performed using a Hologic Discovery v12.6.2 instrument (Hologic, Inc, Bedford, Massachusetts). Bone mineral density was measured in the lumbar spine. If that was not possible due to hardware, measurement was at the femoral neck or 33% radius, based on the patient's contractures.

Additional data elements were fracture history, dystrophin gene mutation analysis, muscle biopsy results and age of onset of muscle weakness.

All data were extracted from the patients' Electronic Medical Record by 1 investigator (AZ) and cross-checked by another investigator (ASR).

C. Statistical Analyses:

We adjusted raw areal bone mineral density measurements for both chronological-age and bone-age. Raw areal bone mineral density measurements in gram/cm^2 were compared with bone mineral density measurements from *chronological-age*, race and sex-matched standard controls to produce traditional z-scores. These z-scores were not adjusted for height. To generate z-scores adjusted for bone age, we assigned each patient an adjusted birth date based on bone age obtained by wrist x-ray. We then inputted this adjusted birth date into the DXA software to generate an adjusted z-score based on comparison of raw areal bone density with that of a control population matched for *bone-age*, race and sex. We compared z-scores based on chronological age to those adjusted for bone age.

Statistical analyses were conducted using SAS for Windows, version 9.3 (SAS Institute Inc., Cary, North Carolina) and statistical significance was defined as a *P*-value less than 0.05.

3. Results

We report DXA results from 12 patients with DMD tested between 12 and 23 years of age (mean 15.5 ± 3.1 years). All patients were on glucocorticoid therapy (5 on prednisone, 4 on deflazacort, 2 had been on prednisone in the past and were now on deflazacort, 1 had been on prednisolone in the past and was now on deflazacort), for a duration of 6.5 to 14.0 years (mean 10.0 ± 2.3 years). Of the 12 patients, 6 were non-ambulatory and 5 were treated with antiresorptive therapy (bisphosphonate or denosumab) for 1.4 to 11.4 years (mean 5.8 ± 2.4 years). One patient (Patient 3) was treated with testosterone and no other patients were treated with any growth or puberty enhancing agents. The general

characteristics of the patients are summarized in Table 1 and additional data is summarized in Table 2.

Bone mineral density was measured at the lumbar spine in 10 patients, femoral neck in 1 patient (due to spine hardware preventing measurement in the spine) and 33% radius in 1 patient (due to spine hardware and hip contractures preventing measurement in the spine and hip, respectively). Bone age at the time of the DXA scan was significantly lower than chronological age (mean age 13.0 versus 15.5 years respectively; p 0.04). Bone mineral density adjustment for bone age rather than chronological age resulted in higher z-scores for all patients (Table 1 and Figure 1) with an average difference of 1.0 $\pm$ 0.5 in the 10 z-score measurements at the lumbar spine.

4. Discussion

Our series shows a considerable delay in skeletal maturation in these 12 patients on glucocorticoid therapy for DMD, as demonstrated by their delayed bone age. The mean difference between chronological and bone age in our study was 2.5 years, which is slightly lower than the 3 to 6 year delay previously described by Mayo et al.⁹ In parallel, bone mineral density adjustment for bone age in this series yielded higher z-scores for all patients compared to bone mineral density adjustment for chronological age.

Bone mineral density evaluation in children and young adults is reported as a z-score rather than a t-score as these patients have not yet accrued their maximal bone density, so it would not be appropriate to compare their bone mineral density to that of a healthy reference population. Rather, z-scores are determined by comparing bone mineral density values to those of a chronological age, sex and ethnicity-matched reference population.¹² Despite this adjustment, the resulting z-score is still confounded by several factors, including delays in growth and sexual maturation in the patients of interest compared to the healthy reference population, as is often seen in patients with DMD. As a result, bone mineral density adjustment for chronological age may still overestimate these patients' actual bone mineral deficit, and an argument can be made that these patients are better compared to a population with more congruent bone size and sexual maturation.

Correction of bone mineral density measurement for height-for-age presents one possible solution to address this shortcoming^{6,13} but accurate height measurements are not possible in patients who are wheelchair bound or who have severe contractures. While ulna length, forearm length, arm span, tibia length, knee height and segmentally measured recumbent length have been used for the prediction of height, none have been validated in the DMD population and these methods also have limitations.^{14–16} We thus propose the use of bone age rather than chronological age for the adjustment of bone mineral density in glucocorticoid-treated patients with DMD as an alternate descriptor of their bone mineral status. Interestingly, using bone age rather than chronological age resulted in higher z-scores for all patients. This is of particular relevance since DXA is no longer recommended for osteoporosis screening in this patient population because of variability in z-scores depending on the reference database and its failure to predict fractures.⁷ We argue that this may be due to choosing an inappropriate reference database, and that perhaps using bone age rather than

chronological age may provide more meaningful results. Furthermore, not only is DXA still utilized to monitor the trajectory of bone health by serial bone mineral density measurements, but it is also described as an “emerging method for at risk populations” in the current care considerations,⁷ so improving the validity and accuracy of this tool is important.

Our study has several limitations. Because it is a retrospective study using available clinical testing, the sample size is small as relatively few patients had simultaneous DXA and bone age results available for review. In addition, our patients were heterogeneous in terms of age, duration of disease, duration of glucocorticoid use, and bisphosphonate use. DXA examination sites were also heterogeneous, as we could not utilize the lumbar spine in 2 patients. Finally, the importance of measuring bone mineral density in patients with DMD relates to fracture risk assessment. Due to the small size and relatively short observation period of our study, we cannot comment with certainty on whether or not the use of bone age rather than chronological age for adjustment of bone mineral density in glucocorticoid-treated patients with DMD provides a better estimation of fracture risk. We believe that additional research to answer this question will be important.

In conclusion, we present preliminary data based on a small, heterogeneous group of males with DMD that highlights the lack of clarity in interpretation of bone mineral density scores in this population and suggests additional research is needed to determine the best way to predict fracture risk in this patient group.

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Abbreviations

5.

BMI	Body Mass Index
DXA	Dual X Ray Absorptiometry
DMD	Duchenne Muscular Dystrophy

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Figure 1. Z-scores based on chronological and bone age for individual patients.
 Bone Mineral density adjustment for bone age rather than chronological age resulted in higher z-scores for all patients.

Table 1:

General characteristics and adjusted z-score of study patients

Patient	CA, yr	BA, yr	BMI, kg/m ²	Duration of Fulltime Wheelchair Dependence, yr	Duration of GC use, yr	GC Used	Total Testosterone, ng/dL ^a	Duration of AR use, yr	DXA Site Assessed	Z-score based on CA	Z-score based on BA
1	15.4	13.0	21.6	4.7	9.6	Prednisone	<5 ^b	6.7	Femoral neck	-4.3	-4.1
2	17.5	12.5	25.0	6.9	11.4	Deflazocort	N/A ^c	6.9	L1-L4	-1.3	+1.3
3	22.7	18.0	27.7	9.4	14.0	Prednisone, Deflazocort	388 ^d	7.3	L1-L3	-2.3	-1.6
4	18.6	17.0	45.7	7.1	12.2	Prednisone	147 ^b	6.7	1/3 distal radius	-6.0	-5.3
5	18.0	12.5	38.0	N/A ^e	11.2	Deflazocort	N/A ^c	N/A	L1-L4	-3.3	-1.0
6	14.1	13.0	31.4	2.3	9.3	Deflazocort	<5 ^b	N/A	L1-L4	-3.4	-2.7
7	13.3	11.0	23.5	N/A ^e	9.8	Deflazocort	N/A ^c	N/A	L1-L4	-1.6	-1.2
8	13.0	11.6	20.62	2.6	9.9	Prednisone	35 ^b	N/A	L1-L4	-2.4	-2.1
9	11.9	11.6	17.3	N/A ^e	7.7	Prednisolone, Deflazocort	<5 ^b	N/A	L1-L4	-2.5	-2.4
10	12.1	11.6	26.6	N/A ^e	7.1	Prednisone	<5 ^b	N/A	L1-L4	-1.1	-0.9
11	13.0	11.6	25.7	N/A ^e	6.5	Prednisone	N/A ^c	1.5	L1-L4	-0.8	+0.2
12	16.4	13.0	32.0	N/A ^e	12.4	Prednisone, Deflazocort	<5 ^b	N/A	L1-L4	-3.1	-1.4
Mean (SD)	15.5 (3.1)	13.0 (2.1)	27.9 (7.9)	5.5 (2.6) ^f	10.0 (2.3)	-	-	5.8 (2.4) ^f	-	-	-

Abbreviations: AR: antiresorptive, BA: bone age, BMI: body mass index, CA: chronological age, DXA: dual x-ray absorptiometry, GC: glucocorticoid

^aNormal Range: 10–11 years: 3–237 ng/dL; 12–13 years: 29–432 ng/dL; 14–15 years: 40–778 ng/dL; 16–18 years: 238–1048 ng/dL.^bTestosterone checked within 5 months of reported DXA result.^cTestosterone not checked, however physical exam and history demonstrated delayed puberty.^dThis patient was started on testosterone therapy two years prior to reported DXA result due to a total testosterone of 106 ng/dL.^eThese patients were not fully wheelchair dependent at the time of DXA.^fFor these variables, the mean was calculated for the patients who were fully wheelchair dependent or on antiresorptive therapy.

Table 2:

Additional characteristics of study patients

Patient	Dystrophin Gene Mutation	Muscle Biopsy Result	Age of onset of muscle weakness	Age, yr	Fracture site	Fracture History	Cause
1	Premature stop in exon 65	Absence of dystrophin	9 months	12	Proximal femur		Rollled in bed
				13	Distal femur		Unknown
2	Frame shift mutation in codon 84	Absence of dystrophin	5 years	16	Proximal femur		Fell from wheelchair
3	Premature stop in exon 53	Not performed	2 years	14	Distal femur		Fell from wheelchair
4	Deletion of exons 45–50	Not performed	3 years	none	None		None
5	Premature stop	Absence of dystrophin	2 years	none	None		None
6	Deletion of exons 48–52	Not performed	4 years	10	Distal tibia		Struck by falling child on trampoline
				7	Elbow		Fell off horse
				12	Lumbar and thoracic spine compression fractures		Found on screening x-ray
7	Deletion of exon 19	Not performed	16 months	14	Lumbar spine compression fracture		Found on screening x-ray
8	Deletion of exons 48–52	Not performed	2 years	12	Lumbar and thoracic spine compression fractures		Found on screening x-ray
9	Deletion of exon 19	Not performed	2 years	3	Wrist		Unknown
				12	Proximal femur		Held down during diaper change
10	Deletion of exons 48–52	Not performed	2 years	2	Arm (unknown site)		Jumped off furniture
				14	Femur		Jumped off furniture
11	Duplication of exons 46/47	Not performed	3 years	17	Femur		Tripped while walking
				17	Lumbar and thoracic spine compression fractures		Found on screening x-ray
12	Stop codon in exon 20	Not performed	1 year	Unknown	Foot (unknown site)		Stress Fracture
					Lumbar and thoracic spine compression fractures		Found on screening x-ray