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Bone health measures in glucocorticoid-treated ambulatory boys with Duchenne muscular dystrophy

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Abstract

Osteoporosis is a major problem in boys with Duchenne Muscular Dystrophy (DMD), attributable to muscle weakness and glucocorticoid therapy. Consensus regarding bone health assessment and management is lacking. Lumbar spine areal bone mineral density (defined as bone mass per area of bone) by dual-energy X-ray absorptiometry (DXA) is frequently the primary measure used, but has limitations for boys with DMD. We retrospectively studied 292 ambulant glucocorticoid-treated boys with DMD categorized by functional mobility score, FMS 1, 2 or 3. We assessed DXA whole body and lumbar spine areal bone mineral density and content Z-scores adjusted for age and height, lateral distal femur areal bone mineral density Z-scores, frequency of fractures, and osteoporosis by International Society for Clinical Densitometry 2013 criteria. Whole body and femoral DXA indices decreased, while spine fractures increased, with declining motor function. Lumbar spine areal bone mineral density Z-scores appeared to improve with declining motor function. Bone mineral content Z-scores were consistently lower than corresponding bone mineral density Z-scores. Our findings highlight the complexity of assessing bone health in boys with DMD. Bone health indices worsened with declining motor function in ambulant boys, but interpretation was affected by measure and skeletal site examined. Whole body bone mineral content may be a valuable measure in boys with DMD. Lumbar spine areal bone mineral density Z-score as an isolated measure could be misleading. Comprehensive management of osteoporosis in boys with DMD should include vertebral fracture assessment.

Keywords: Dual-energy X-ray Absorptiometry (DXA); Bone mineral content; Bone mineral density; Osteoporosis; Fracture; Steroid

1. Introduction

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive muscle disease due to lack of dystrophin, which occurs in approximately one in 3500 to 5000 live male births [1]. Osteoporosis is a major problem in boys with DMD: it is caused by intrinsic risk factors, including progressive muscle weakness and immobility, and is also associated with the use of long term glucocorticoid therapy [2–13]. Glucocorticoid therapy preserves motor and cardiopulmonary function, but causes osteoporosis by decreasing bone formation, increasing bone resorption, and delaying or inhibiting puberty.

In glucocorticoid-naïve boys with DMD, areal bone mineral density (aBMD) of the lumbar spine is significantly decreased after loss of ambulation, and aBMD of the proximal femur is severely decreased even when gait is minimally affected [13]. In a cross-sectional study of glucocorticoid-treated boys with DMD (24 patients, aged two to 19 years, 9 non-ambulatory), aBMD of total body, spine, hip, heel and forearm skeletal sites was lower than that of age-matched controls, the differences increasing with age [14]. We have previously shown that aBMD of the lateral distal femur in glucocorticoid-treated boys decreases with worsening motor function [15]. However, these reports are limited by small sample size and study design, and

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are unable to demonstrate correlation of changes in aBMD (or other bone health measures) with disease progression.

Low bone mineral density results in increased fracture risk [16], and vertebral compression fractures have been reported to occur in up to 44% of glucocorticoid-treated patients [17]. One study of pediatric patients with neuromuscular disorders (including DMD) found a 6–15% increased risk of fracture with each 1.0 decrease in aBMD Z-score of the distal femur [18]. Fractures of lower-extremity long bones in boys with DMD frequently result in permanent loss of ambulation [13].

Bone health in boys with DMD is typically assessed by dual-energy X-ray absorptiometry (DXA) measurement of aBMD (calculated by dividing bone mineral content [BMC] by bone area) of the lumbar spine [13,14,19–22]. A DMD care considerations working group recommended obtaining a baseline DXA scan at the start of glucocorticoid therapy, followed by annual scans in at-risk patients: those with a history of fractures, on long term glucocorticoid treatment, or who have low DXA Z-scores (more than −2 standard deviations below the mean) [23]. Clinicians and researchers recognize the limitations of assessing aBMD by DXA in growing bones in children and adolescents: adjustment for height, or even better for height-adjusted Z-score, or bone mineral apparent density (BMAD) for the spine, is recommended [24–27]. Some advocate for the use of BMC instead of bone mineral density [28,29]. In boys with DMD, aBMD assessment by DXA, when expressed as Z-scores that adjust for age relative to the normal population, can be problematic because of decreased growth rate and delayed bone age secondary to long term glucocorticoid use. Even using Z-scores that adjust for height as well as age, in an attempt to account for poor growth, may not be adequate. Spine deformities, including lordosis, scoliosis and kyphosis, and contractures affecting postural alignment may result in inaccurate height measurements, thereby affecting height-adjustment of aBMD Z-scores. Lumbar vertebral compression fractures may decrease bone area, resulting in artifactual elevation of aBMD of the lumbar spine. However, current recommendations for DMD care (at the time of writing this paper) do not include routine assessment for vertebral fractures [23,30]. Furthermore, the recent criteria published in 2013 by the International Society for Clinical Densitometry (ISCD) for defining osteoporosis in pediatrics (requiring the presence of vertebral compression fractures, or a clinically significant long bone fracture history with an aBMD Z-score ≤ −2.0) have yet to be incorporated into DMD guidelines [30].

It is essential to be able to accurately assess bone mineral accrual, and to relate these measures to the stage of disease, to guide decisions regarding prevention and treatment of osteoporosis in boys with DMD. We hypothesized that bone health in ambulatory boys with DMD worsens with disease progression, as measured by functional mobility status (FMS 1, 2 and 3) [31]. We examined DXA indices, aBMD and BMC of whole body and lumbar spine sites, and aBMD of the lateral distal femur, as well as frequencies of long bone and vertebral fractures, and frequency of osteoporosis as defined by the 2013 ISCD criteria [30].

2. Patients and methods

We conducted a retrospective chart review of boys with DMD seen during the period from January, 2005 to July, 2012 at the Cincinnati Children's Hospital Medical Center (CCHMC) Neuromuscular Comprehensive Care Center. Patients and families gave consent/assent for clinical data to be recorded in an Institutional Review Board-approved neuromuscular database.

A total of 292 ambulant glucocorticoid-treated boys with DMD boys were identified and grouped by worsening functional mobility score (FMS 1, 2 or 3), a measure that has been used consistently over the study period. FMS 1, 2 and 3 were defined according to Swinyard and Deaver's 8-grade scale: FMS 1, mild abnormalities in gait, able to climb stairs without assistance; FMS 2, more apparent gait abnormalities, requires a railing or other support for stairs; FMS 3, walks and arises from a chair independently, but cannot negotiate stairs without help [31]. This functional mobility scale was used in previous bone health studies of boys with DMD [13,15]. Inclusion criteria were male sex, diagnosis of DMD (confirmed by genetic mutational analysis and/or muscle biopsy showing lack of dystrophin), glucocorticoid use, ambulatory (FMS 1, 2 or 3), and ages 5 to 18 years. Patients were excluded if they were on bisphosphonate therapy at the time of the DXA scan or had previously been on bisphosphonate therapy. In accordance with our center's bone health protocol, all boys underwent annual assessment to ensure adequate calcium and Vitamin D intake, 25-hydroxyvitamin D and urine calcium monitoring, and DXA and spine radiographic imaging.

2.1. Outcomes

Primary outcomes of interest for this study were differences in whole body (including head) and lumbar spine aBMD and BMC, and lateral distal femur aBMD, as measured by DXA. Abbreviations for DXA measures are listed at the end of this article. DXA scans were performed using Hologic Discovery A (S/N 81400) software, version 12.7.3.1, and analyzed using Apex 2.3 software. The coefficient of variation for the whole body DXA scans was less than 1%, and the coefficient of variation for the lumbar spine DXA scans was 1%. The coefficient of variation for the distal femur DXA scans was unknown due to the exploratory nature of these types of scans. Age-adjusted Z-scores (Z), and height- and age-adjusted Z-scores (HAZ) for whole body and lumbar spine skeletal sites were derived using normal values for ages 5 to 20 years [32]. Standing heights were obtained on all boys using a Harpenden stadiometer and were used to adjust whole body and lumbar spine Z-scores for height (HAZ) [32]. For the lateral distal femur, age-adjusted Z-score equations were only available for aBMD for children of ages 6–18 years [33]. Other bone health outcomes recorded were frequency of long bone and spine fractures, from which the frequency of osteoporosis according to ISCD 2013 criteria was derived [30]. Spine fractures were assessed by routine annual screening with anterior-posterior and lateral thoracic and lumbar radiographs. The presence or absence of spine fractures was assessed and reported by a