A portrait of the bone mineral density of boys with Duchenne muscular dystrophy

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Abstract

Introduction Duchenne muscular dystrophy (DMD) patients are at risk of developing conditions that can compromise their bone health, such as fractures and walking impairment. We aimed to assess bone mineral density as a function of the age of DMD patients. **Materials and Methods** The cross-sectional study included 48 participants. Bodyweight and height were collected to determine the height-for-age and BMI-for-age Z-scores. Lumbar spine (LS) and total body (TBLH) bone mineral density (BMD) measurements were performed with dual-energy X-ray absorptiometry. Height-for-age Z-scores (HAZ) of boys under 19 years-old were determined, and the BMD was adjusted for HAZ. **Results** The DMD patients' HAZ curve is on the left compared to the WHO standard. The older patients had lower LS-BMD ($p = 0.012$) and TBLH-BMD ($p < 0.001$) Z-score values than younger patients. There was a moderate negative correlation between age and the LS-BMD Z-score ($\rho = -0.49$, $p < 0.001$), a strong negative correlation between age and the TBLH-BMD Z-score ($\rho = -0.82$, $p < 0.001$), and a moderate positive correlation between age and the TBLH-BMDHAZ ($\rho = 0.43$, $p = 0.007$). **Conclusion** For clinical evaluation DMD population, it is necessary to consider the variables related to height since the delay in linear growth may underestimate the BMD Z-scores. DMD patients have impaired linear growth, and older boys could have more severe bone morbidity.

Introduction

Duchenne muscular dystrophy (DMD) is an autosomal-recessive disorder on the X chromosome defined by mutations in the dystrophin gene, leading to severe deficiency in dystrophin protein [1]. When there is some dystrophin production, the disease is classified as Becker muscular dystrophy [2]. Dystrophin stabilizes skeletal and cardiac muscle by connecting actin in muscle fibers to the extracellular matrix; in the absence of dystrophin, recurrent muscle fiber injury leads to chronic inflammation, changes in body composition, and weakness [3]. Additionally, patients with this condition have cardiorespiratory complications and attend impaired bone health with disease progression [4].

Several clinical trials have evaluated the safety and efficacy of gene replacement therapies, exon skipping, readthrough therapy, anti-inflammatory compounds, myostatin inhibitors, and cardioprotective compounds [5]. Nonetheless, corticosteroids are the most widespread pharmacological treatment for DMD. Corticosteroids improve muscle strength and function in boys with DMD. However, glucocorticoid therapy predisposes osteoporosis by decreasing bone formation and increasing bone resorption, growth, and pubertal delay. The proximal femur and spinal vertebrae in boys with DMD show markedly reduced bone mineral density (BMD) [6].

The low BMD results in a high incidence of fragility fractures, which greatly impairs DMD populations' function and quality of life [7]. Vertebral fractures have significant consequences of chronic back pain and spinal deformities, like scoliosis, while lower long bone fractures precipitate a permanent loss of ambulation in 20% to 70% of DMD patients [8].

Thus, the importance of assessing bone mineral density in DMD patients is evident. This parameter must be evaluated to establish adequate bone health management and prevent fractures, spinal deviations, and bone pain. Therefore, this study aims to assess bone mineral density as a function of the age of DMD patients.

Materials And Methods

Research Design

This study is an observational, cross-sectional survey approved by the Ethics Committee (CAAE: 57345516.0.0000.5292) as determined by Brazilian National Health Council. Written informed consents were obtained from participants and their parents/guardians. The study included male DMD/ Becker patients who were seen in the neurology outpatient clinic in Onofre Lopes University Hospital from October 2016 to October 2019.

The inclusion criteria were a confirmed genetic diagnosis of DMD/ Becker and an age equal to or greater than five years. The use of bisphosphonates was the exclusion criterion. The study population (n=48) was distributed into the following two subgroups by age for classification according to World Health Organization growth curves [9, 10]. Group 1 (G1) was 5 to 19 years-old, and group 2 (G2) was above 19 years-old.

Anthropometric Assessment

Bodyweight (kg) and height (cm) were measured using an electronic scale (BK50F, Balmak, Brazil) and a stadiometer (ES2030, Sanny, Brazil), respectively. A digital platform scale was used for participants who could not ambulate to measure their body weight (KN P/R500/50, KN Waagen, Brazil). Height was estimated by measuring their recumbent height using an inelastic tape, measured from the top of the head to the base of the feet [11]. BMI was calculated as the participant's body weight (kg) divided by their height squared (m^2).

This study determined height-for-age (HAZ) and BMI-for-age Z-scores using the WHO AnthroPlus v1.0.4[®] software. The anthropometric evaluation was based on height-for-age (5 to 19 years-old) and BMI-for-age Z-scores (5 to 19 years-old) or BMI classification (>19 years-old), as recommended by the World Health Organization [9,10].

Bone mineral density and patients' clinical history of bone fractures

Bone mineral density (BMD) was assessed in the lumbar spine (LS), from vertebrae L1 to L4, and the total body less head (TBLH). BMD was measured using a DXA (Lunar DPX NT, General Electric Company, USA)

with pediatric evaluation software to correct body size. A trained technician performed the examination, and the participants wore light clothing free of metal fasteners. The data are expressed as measurements in g/cm² and Z-scores. For the analysis, a Z-score of ≤ -2.0 indicated low BMD, as suggested by the International Society for Clinical Densitometry (ISCD, 2019) for young, adolescent, and adult males [12]. The height-for-age Z-score (HAZ)-adjusted BMD Z-score (BMDHAZ) was calculated as described by Zemes et al. (2011) for those participants above 19 years-old [13].

Participants or their guardians reported their clinical history of bone fractures during anamnesis. Information on the previous occurrence of bone fractures was collected.

Statistical analysis

The data obtained in the study were tabulated and analyzed with Intel SPSS v28[®] software. Additionally, the Shapiro-Wilk test was used to assess the normality of the data, and the data are presented as descriptive measures (mean $\pm$ standard deviation, or median and interquartile range). To analyze BMD as a function of the age of DMD patients, we compare G1 and G2 using the Mann-Whitney U Test. Then, Spearman Rank Order Correlation (ρ) tests were performed between the BMD Z-scores and age. After that, the Standard multiple regression was used to assess the ability of two control measures (age and height) to predict BMD Z-scores (LS-BMD, TBLH-BMD).

Preliminary analyses were conducted to ensure no violation of normality, linearity, multicollinearity, and homoscedasticity assumptions. We removed extreme values (outliers) before this analysis procedure when detected. The results were considered statistically significant when $p < 0.05$.

Results

In total, 48 participants aged between 5 to 24 years were recruited for this study. Exonic deletions were present in 56% of *DMD* genetic tests, and the other participants presented duplications, insertions, or base substitutions.

Regarding the HAZ, 41% of G1 participants were classified as short stature. This index is not applicable for groups above 19 years-old. The comparison between the DMD HAZ curve and WHO standard curves is shown in Figure 1. Regarding BMI assessment, half of the DMD patients evaluated were eutrophics, but we found a greater frequency of thinness/underweight in older participants. The anthropometric characteristics of the study population are presented in Table 1.

In total, 19 participants walked independently, all in the younger group. These participants frequently used glucocorticoids (prednisone), while only two in G2 used glucocorticoids. Regarding the bone fractures clinical history, two participants in G1 reported a history of fractures, both of which occurred in the femur. Four participants in G2 had bone fractures in different regions: the humerus, the femur, the

fibula, and the ankle and knee. No patient reported a clinical history of vertebral fractures. The clinical characteristics of the study population are presented in Table 1.

A Mann-Whitney U Test revealed a significant difference between the groups in the LS-BMD and TBLH-BMD (Table 2). There was a negative correlation between LS-BMD Z-score and age ($\rho = -0.49$, $n = 48$, $p < 0.001$), between TBLH-BMD Z-score and age ($\rho = -0.82$, $n = 48$, $p < 0.001$), and a positive correlation between TBLH-BMDHAZ and age ($\rho = 0.43$, $n = 38$, $p = 0.003$). There was no correlation between LS-BMDHAZ and age ($\rho = -0.15$, $n = 35$, $p = 0.203$). Standard multiple regression was used to assess the ability of two control measures (age and height) to predict BMD Z-scores (Table 3).

Discussion

The severity of osteoporosis in DMD correlates with the age of patients, even when bone size was adjusted. The adjustment is necessary because BMD can be underestimated in DMD patients because of their short stature. Ward et al. (2018) described the technique to correct BMD Z-score, taking into account the HAZ, which was used here [14].

In this study, the BMI results corroborated the susceptibility of DMD patients to overweight and obesity (Table 1). Adipose tissue is associated with the production of inflammatory cytokines, which can negatively affect bone metabolism. On the other hand, adipose tissue also has an indirect positive effect on bone metabolism by producing hormones, cytokines, and adipokines, such as circulating leptin and insulin. These substances stimulate bone formation [15]. Given that this tissue affects bone metabolism differently, it is suggested that the prevalence of overweight and obesity is not the main determining factor for bone loss in the population studied.

Short stature was observed in almost half of participants under 19 years-old. Although there is no appropriate classification for the height of people over 19 years-old, shallow values can be observed in this study. The etiology of short stature in populations with DMD is still unclear. However, previous studies suggest that low levels of growth hormones and the loss of muscle tone are partly responsible for short statures in DMD patients [16].

Additionally, the long-term glucocorticoid treatment affects DMD boys' growth [17]. The continuous use of glucocorticoids is also related to pubertal delay and weight gain. These factors are associated with the incidence of fractures, osteoporosis, and the early loss of walking [18,19–22]. Moreover, height outcomes can be predicted by genetics. Distal deletions and central mutations of the DMD gene are associated with short stature [23].

In G1, 82.1% of the participants used glucocorticoids. With the progression of the disease and muscle loss, the adverse effects on patient health caused by the chronic use of glucocorticoids may be more clinically relevant than the potential benefits [24]. The use of glucocorticoids inhibits the production of factors that regulate the hypothalamic-pituitary axis during puberty, leading to a decrease in growth hormone production, and resulting in pubertal delay [25].

One of the main findings of this study was that both LS-BMD and TBLH-BMD Z-scores were negatively correlated with age in the study population. These findings were corroborated by the significantly higher median BMD Z-score values in the participants aged 5.0 to 19 years (G1).

On the other hand, TBLH-BMDHAZ was positively correlated with age. However, the scatterplot analysis shows that the two variables are nonlinearly related (Figure 2 - D) before and after 15 years-old. It is possible to notice that TBLH-BMDHAZ, being a variable adjusted for HAZ, follows a straight line following the linear bone growth of children/adolescents, despite the bone losses observed in this population. Regarding LS-BMDHAZ, a variable also adjusted for HAZ, no correlation with age was observed, possibly due to the bone characteristic of L1-L4.

Given the possible misinterpretation generated only by the correlation analyses, this study showed the relative contribution of age and height on the dependent variables evaluated. Thus, to assess individuals with DMD, height and age are crucial information for clinical practice. Furthermore, nutritional complications get worse with age [23]. This interrelationship may be related to the mechanical load of skeletal muscles on the bones of the entire body having decreased due to the loss of muscle function over time. Larson et al. [26] compared the LS-BMD and the proximal femur-BMD in DMD patients, and there was a significantly larger reduction in the femur-BMD than in the LS-BMD. This was affected when the patients lost the ability to walk, while that of the proximal femur-BMD was low even before they lost the ability to walk.

The results of our study indicated that older DMD patients might have a more marked impairment in BMD than younger patients, both in the LS and in the TBLH. Tung et al. [17], Mayo et al. [27], and King et al. [28] assessed LS-BMD and TBLH-BMD in boys aged between 8.5 to 17 years and have shown results that are like ours. The damage to muscle fibers present in DMD patients is related to chronic inflammation of the muscles and the release of inflammatory cytokines, which impair the function of the cells involved in forming bone tissue. This damage can contribute to bone loss in DMD patients [29].

Decreases in LS-BMD and TBLH-BMD are related to an increase in the risk of vertebral and long bone fractures, respectively, in DMD patients. Vertebral fractures cause spinal deformity, chronic pain, difficulty sitting, and decreased lung function, and long bone fractures may be associated with the permanent loss of ambulation [30].

According to a study by Ma et al. [31], approximately 20 to 60% of boys with DMD experienced low-trauma extremity fractures (usually of the femur or distal tibia), making it difficult or impossible for them to walk. Additionally, the risk of fractures increases as DMD patients' survival increases [23]. In agreement with the results of previous studies, the older patients in this study (G2) had a high prevalence of reported bone fractures (44.4%), which may be associated with the TBLH-BMD Z-score being lower in this group. Among these fractures, there is a predominance of long bone fractures. No patient reported a clinical history of vertebral fractures. Vertebral fractures can be asymptomatic in their early phases and thus undetected in the absence of monitoring [14].

A few participants in this study could walk independently. The early loss of ambulation caused by the

disease's progression gradually decreases these participants' physical activity. The skeletal system has great modeling and remodeling dynamics as it adjusts its properties in response to the load applied to it. Therefore, bone loss occurs when there is a decrease in muscle use [32,33]. Studies have shown that decreased muscle function and aging directly contribute to decreased bone density in DMD patients [34], which is consistent with our results.

One of the strengths of our study is the sample size, which is larger than those of other studies that have also evaluated bone density in DMD patients [18,28,31]. Additionally, most studies have exclusively evaluated the LS-BMD or TBLH-BMD, and in our study, BMD was evaluated in both areas, and we adjusted these scores for HAZ.

The study has some limitations. As it is cross-sectional, it was impossible to analyze the cause-effects among glucocorticoids, walking ability, BMD, and disease progression. Also, at the time of the data collection, the sexual maturation stage was not a collected variable; therefore, we will not be able to provide this information. In addition, it is important to assess BMD associated with the assessment of bone fractures by imaging tests. Thus, longitudinal design studies should be conducted to evaluate the influence of these variables.

It is concluded that for clinical evaluation of the DMD population, it is necessary to consider the variables related to height since the delay in linear growth may underestimate the BMD Z-scores. DMD patients have impaired linear growth and older boys could have more severe bone morbidity. These findings reinforce the relevance of assessing bone health in these patients at young ages to establish the most appropriate therapy and prevent bone fractures, as well as delay the early loss of walking and occurrence of fractures.

Declarations

Authors' contributions: All authors contributed to the execution of this study. SHLV and LCL wrote the manuscript. ACMM, ECG, and SHLV contributed to the study design and data analysis. LCL, ECG, TAC, and BGMA contributed to the subject briefings and data collection. ACMM, JBN, and SHLV contributed to the interpretation of the data.

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Conflicts of interest: None of the authors has any conflict of interest to disclose.

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Tables

Table 1. Characterization of Duchenne muscular dystrophy patients (n=48), according to age groups: G1, 5.1 to 18.7 years-old; G2, 19.1 to 24.7 years-old.

Variables	G1 (n=39)	G2 (n=9)
Age (years)*	10.5 (8.2,14.0)	19.8 (19.3, 19.8)
Weight (kg)*	26.5 (21.6, 38.8)	47.2 (34.6,59.4)
Height (cm)*	131.6 (122.0, 143.0)	149.2 (143.0, 155.5)
Height-for-age (Z-score)*,§	-1.23 (-2.51, -0.64)	NA
Short stature (n (%))	16 (41.0)	NA
Adequate stature (n (%))	23 (59.0)	NA

BMI (kg/m ²)*,¶	16.3 (14.5, 23.0)	21.6 (17.8, 25.9)
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BMI-for-age (Z-score)*,§	0.10 (-2.54, -0.64)	NA
Thinness / Underweight (n (%))	5 (12.8)	2 (22.2)
Eutrophy (n (%))	20 (51.3)	4 (44.4)
Overweight/ Obesity (n (%))	14 (35.9)	3 (33.3)
Independent walking (n (%))	19 (48.7)	0 (0)
Use of glucocorticoids (n (%))	32 (82.1)	2 (22.2)
Bone fractures (n (%))	2 (5.1)	4 (44.4)
*Date presented as Median (Q1, Q3); §classification for participants aged 5 to 19 years (n=39); ¶classification for participants aged > 19 years (n=9); NA: Not applicable; BMI, body mass index.		

Table 2. Comparison between the lumbar spine bone mineral density and total body less head bone mineral density of Duchenne muscular dystrophy patients (n=48), according to age groups: G1, 5.1 to 18.7 years-old; G2, 19.1 to 24.7 years-old.				
	G1 (n=39)	G2 (n=9)	p*	r
LS-BMD (Z-score)	-1.4 (-1.9, -0.4)	-3.2 (-3.6, -1.5)	0.012	0.36 [#]
TBLH-BMD (Z-score)	-1.2 (-1.8, -0.6)	-2.9 (-3.4, -2.6)	<0.001	0.57 ^{&}
LS-BMDHAZ	-0.6 (-1.0, -0.3)	–	–	–
TBLH-BMDHAZ	-0.2 (-0.4, -0.1)	–	–	–
LS-BMD: lumbar spine bone mineral density (L1-L4); TBLH-BMD: total body less head bone mineral density. LS-BMDHAZ: LS-BMD adjusted for height-for-age Z-score. TBLH-BMDHAZ: TBLH -BMD adjusted for height-for-age Z-score. *Mann-Whitney U Test (statistically significant: p <0.05). r = size effect (Cohen (1988) criteria: [#] small effect, ^{&} large effect)				

Table 3 is available in the supplementary files.

Figures

Figure 1

Comparative between height-for-age Z-score curves. Values for Duchenne muscular dystrophy patients were plotted in the red line, and the World Health Organization standard is in the green line. (Image: WHO AnthroPlus software)

Figure 2

Strength and direction of the relationship between A) LS-BMD: lumbar spine bone mineral density Z-score and age; B) TBLH-BMD: total body less head bone mineral density Z-score and age; C) LS-BMDHAZ: LS-BMD adjusted for height-for-age Z-score and age; D) TBLH-BMDHAZ: TBLH-BMD adjusted for height-for-age Z-score and age. ρ : Spearman Rank Order Correlation test was statistically significant if $p < 0.05$. A and B ($n = 48$); C ($n = 35$); D ($n = 38$).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table3.jpg](#)