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Height adjustment reduces occurrence of low bone mineral density in children and adolescents with HIV

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SUMMARY

OBJECTIVE: The aim of this study was to quantify the reduction of bone mineral density with and without height adjustment.

METHODS: A cross-sectional study was performed with 69 Brazilian children and adolescents vertically infected by HIV. Bone mineral density was measured by dual-energy absorptiometry in the lumbar spine. Anthropometric, demographic, and clinical variables were analyzed. A specific calculator was used for height adjustment.

RESULTS: The majority of participants (52.2%) were adolescents and did not present with immunological alterations (61%). Reduced bone mineral density (*Z*-score <-1) was present in 23.2% and low bone mass (*Z*-score <-2) in 5.8%. After height adjustment, these occurrences decreased to 11.6% and 0%, respectively. Patients with reduced bone mineral density had a higher mean age and lower body mass index than patients with normal bone mineral density.

CONCLUSION: The occurrence of reduced bone mineral density decreased after adjustment for height.

KEYWORDS: Bone mineral density. HIV. Child. Adolescent. Osteoporosis.

INTRODUCTION

Chronic diseases, such as acquired immunodeficiency virus (HIV) infection, are the main causes of reduced bone mass (BM) during childhood and adolescence[1-3]. Each chronic disease may alter bone metabolism in a specific way, depending on the system affected and associated morbidities and interventions, which may affect BM in different ways and magnitudes[1]. Children and adolescents with HIV are at higher risk for BM loss[2-4].

Although the mechanisms of this loss are not fully understood, monitoring bone health is part of the care of people with HIV[5,6]. Alterations in bone metabolism, nutrient deficiency, and the use of antiviral therapy (ATV), especially protease inhibitors (PIs), have been associated with reduced BM[2,7-9]. With the improvement of ATV and greater ease of access, children with HIV have reached adolescence and adulthood with an increased risk of BM loss due to increased exposure to risk factors throughout life[10-12].

Dual-energy densitometry (DXA) is the method of choice for evaluating BM in children and adolescents by quantifying bone mineral density (BMD)[1]. Its main limitation is the quantification of areal BMD (aBMD). By not measuring volumetric BMD, BM measured by DXA is influenced by bone size, thereby underestimating BM in smaller people and generating false-positive results for low BM[13,14].

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Considering that growth deficit is a frequent situation in children and adolescents with HIV[5], the evaluation of BM by DXA may overestimate the occurrence of low BM. Despite this, most studies on the evaluation of BM by DXA in children and adolescents with HIV did not perform adjustments to minimize the impact of bone size on DXA results. One possible strategy for this purpose is to adjust for height, generating aBMD adjusted for height ($aBMD_{HAZ}$)[15]. Thus, this study aimed to evaluate BMD by DXA in pediatric patients with HIV, quantifying the occurrence of BMD reduction with and without adjustment for height and analyzing associated factors.

METHODS

Study design and participants

This is a cross-sectional study conducted on HIV carriers followed up in the Unified Health System. The inclusion criteria were children and adolescents with vertical HIV who had undergone bone densitometry in the lumbar spine. Incomplete clinical data, and age below 5 years, due to the technical limitations of height adjustment, were considered exclusion criteria. Data collection occurred between February and May 2018.

Sociodemographic variables

Age and Sex. Age was categorized into school age (5–10 years) and adolescent age (11–19 years).

Densitometric variables

Areal BMD (g/cm^2) in the lumbar spine (L1–L4) was performed with DXA Explorer model equipment (Hollogic Inc., Bedford, MA, USA) and transformed into *Z*-score for sex and age by the equipment software (Apex, version 2.1). Subsequently, using the Pediatric Bone Density Calculator tool (available at https://zscore.research.chop.edu/calcpedbonedens.php), the *Z*-score of height for age was adjusted, generating $aBMD_{HAZ}$. Low BMD was considered a *Z*-score ≤-2[16] and reduced BMD a *Z*-score <-1[17].

Anthropometric variables

Weight, height, and body mass index (BMI) were transformed into *Z*-scores for age using a calculator (available at https://www.bcm.edu/bodycomplab/Flashapps/AllDXArefsChartpage.html).

Clinical variables

These categories include viral load (CV), CD4 and CD8 counts, the use of ATV, the use of PI, and clinical category according to the Centers for Disease Control and Prevention (CDC). CD4 was categorized according to the CDC[18] in children under 12 years of age and according to the World Health Organization[19] in older patients. CD4 and CD8 were dosed by flow cytometry.

Statistical analysis

Kolmogorov–Smirnov, Student's *t*, ANOVA, chi-square, and simple and multiple linear regression tests were used. All variables were presented in terms of a parametric distribution. Variables with p≤0.2 in the simple regression were included in the multiple regression. A two-tailed sample power for the comparison of means was calculated, with an alpha error of 5%. The study was approved by the Research Ethics Committee of the University of Blumenau (opinion 020-04).

RESULTS

The study included 69 out of a total of 96 children and adolescents with vertical HIV followed up in the service. Exclusions were due to age <5 years (n=12) and incomplete data (n=15). Table 1 presents the characteristics of the participants. An occurrence of 23.2% of reduced BMD and 5.8% of low BM was observed. With the $aBMD_{HAZ}$ calculation, the occurrence of reduced BMD was 11.6%, half of that found with aBMD (chi-square=29.97; p<0.00001), and the occurrence of low BMD was 0%.

Patients with reduced BMD had higher age and lower BMI. These differences remained after adjustment for height (Table 2). Adolescents (n=36) had lower aBMD and $aBMD_{HAZ}$ than those of schoolchildren (-0.72±1.3 vs. 0.18±1.0; p<0.005 and -0.09±0.98 vs. 0.76±1.0; p<0.05; power of test >90%) and higher aBMD in g/cm^2 (0.741±0.168 vs. 0.551±0.071; p<0.0005; power of test >90%).

We observed a trend of progressive reduction of BM in association with clinical worsening that was less evident after adjustment for height, which reduced progressively throughout the clinical categories (ANOVA p<0.05; power of test <80%) (Figure 1).

Both aBMD and $aBMD_{HAZ}$ correlated negatively with BMI and age (r=-0.39, p<0.001 and r=-0.37, p<0.01 respectively) and positively with CV (r=0.32, p<0.01 and r=0.44, p<0.001), and aBMD correlated positively with height (r=0.32, p<0.01). In multiple linear regression, we observed a positive and independent correlation of aBMD with CV and BMI (R^2 adjusted 0.21; S=1.15; F=9.19; p<0.0005).

DISCUSSION

The adjustment for height minimized the occurrence of BM loss, demonstrating the impact of growth on the quantification of BM by DXA. The magnitude of this reduction is

Table 1. Characteristics of the participants.

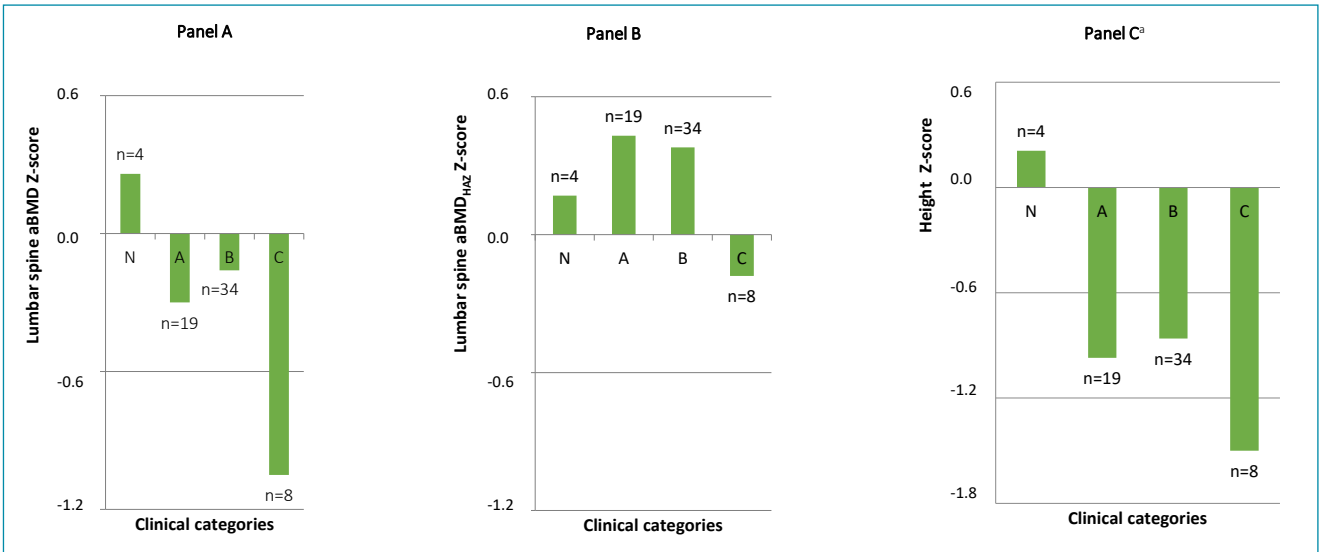
Numerical Variables	Mean±SD	95%CI	Minimum	Maximum
Age (years)	1.5±3.6	9.6 to 11.3	5.0	18.5
Use of ATV (months)	41.1±31.3	33.2 to 49.1	0.0	197.0
CD4 (cells/mm^3)	757.8±429.0	654.8 to 860.9	47.0	2,177.0
BMI (*Z*-score)	-0.4±1.1	-0.7 to -0.2	-4.4	1.6
Weight (*Z*-score)	-0.8±1.1	-1.1 to -0.6	-3.3	1.6
Height (*Z*-score)	-0.9±0.9	-1.1 to -0.7	-2.9	1.1
BMD (g)	0.6±0.2	0.6 to 0.7	0.1	1.2
BMD (*Z*-score)	-0.3±1.3	-0.6 to 0.0	-4.1	3.2
Height adjusted BMD (*Z*-score)	0.3±1.1	0.1 to 0.6	-1.8	3.5
CD8 (cells/mm^3)	1,346.7±667.3	1,181.3 to 1,521.0	317.0	3,642.0
Viral load (copies/mL)	35,196.2±74,883.0	16,179.4 to 52,212.9	0	39,000.0
Categorical Variables	**Frequency (n)**		**Relative Frequency (%)**	
Sex				
Male	33		47.8	
Female	36		52.2	
Age				
Adolescent age	36		52.2	
School age	33		47.8	
Immunologic category				
None or mild suppression	42		60.8	
Moderate suppression	23		33.4	
Severe suppression	4		5.8	
Reduced BMD (*Z*-score <-1)				
Yes	16		23.2	
No	53		76.8	
Low BMD (*Z*-score <-2)				
Yes	4		5.6	
No	65		94.4	
Clinical category[a]				
N	4		6.2	
A	19		29.2	
B	34		52.3	
C	8		12.3	
Use of ATV				
Yes	68		98.6	
No	1		1.4	
Use of protease inhibitors				
Yes	46		70.8	
No	19		29.2	

CD4: cells CD4; BMI: body mass index; BMD: bone mineral density; CD8: cells CD8; ATV: antiviral therapy; [a]Four missing data.

Table 2. Clinical characteristics of the participants according to the bone mineral density status with and without height adjustment.

Variables	Reduced aBMD (n=16)	Normal aBMD (n=53)		Reduced $aBMD_{HAZ}$ (n=8)	Normal $aBMD_{HAZ}$ (n=61)	
	Mean±SD/ n (%)	Mean±SD/ n (%)	p-value	Mean±SD/ n (%)	Mean±SD/ n (%)	p-value
Age (years)	13.5±2.9	9.5±3.5	<0.001[a]	13.4±3.7	10.1±3.6	<0.001[a]
Use of ATV (months)	51.6±28.5	37.8±31.6	NS[a]	32.5±19.9	42.5±32.5	NS[a]
CD4 (cells/mm^3)	616.8±575.8	800.3±370.2	NS[a]	569.1±514.8	779.9±416.4	NS[a]
CD8 (cells/mm^3)	1,252.7±614.4	1,374.8±685.7	NS[a]	1,247.0±802.6	1,360.6±653.2	NS[a]
BMI (*Z*-score)	-1.0±1.5	0.3±0.9	<0.05[a]	-1.0±1.6	-0.4±-1.0	<0.05[a]
Height (*Z*-score)	-0.8±0.9	-1.3±0.8	NS[a]	-1.1±0.9	-0.9±0.9	NS[a]
Use of protease inhibitor	9 (19.6)	37(80.4)	NS[b]	4 (8.7)	42 (91.3)	NS[b]

aBMD: bone mineral density without height adjustment; $aBMD_{HAZ}$: bone mineral density with height adjustment; ATV: antiviral therapy; BMI: body mass index; [a]Student's *t*-test (power of test >75% for age, body mass index, and height, and <75% for the use of antiviral therapy, cells CD4, and cells CD8); [b]Chi-square test.



[a]ANOVA p<0.05, Tukey-Kramer test p<0.02 between categories N and C.

Figure 1. Bone mineral density without and with height adjustment (Panel A and B respectively) and height (Panel C) according to clinical categories.

relevant. While one-fourth of the participants presented with reduced BMD, only one-tenth remained with this diagnosis after adjustment, showing a reduction of over 50%. The same was observed in relation to low BM, whose occurrence disappeared with the adjustment. To date, Jimenez et al.[3] were the only authors who adjusted BMD for height, showing a significant reduction in the occurrence of low BMD (from 15.3% to 4.1%). By adjusting aBMD to volumetric BMD using a mathematical formula, Sudjaritruk et al.[20] also observed a 50% reduction in the occurrence of low BMD in the lumbar spine (from 16.4% to 8.3%). Therefore, the correction for bone size from two different strategies improves the accuracy of DXA in children and adolescents with HIV.

The lower occurrence of decreased BMD generated by adjusting for height is explained by the two-dimensional nature of DXA. This characteristic of the technique underestimates

BMD in small bones, leading to a lack of diagnostic accuracy in short people by not considering bone volume[13,14]. Because of the conditions associated with HIV infection throughout the course of the disease, children and adolescents with HIV have a higher prevalence of short stature [2,9], thus adjusting for height avoids false-positive diagnoses of BM reduction.

Approximately one-fourth of the patients had reduced BMD in the lumbar spine and 5.8% had low BM. The occurrences were 21, 34, and 42%[9,21,22] for reduced BMD and 4, 11, 15%, 16%, and 32% for low BMD[2,3,9,21,23] have been reported. This variability is related to the profiles involved, especially age and clinical category. Studies with older participants[2,22] or those with a predominance of category C[2,9] showed higher rates of impaired BM. When greater age and a predominance of category C are associated, the occurrence of low BM reaches 32%[2]. The occurrences observed in this study are similar to an American study with a similar clinical profile[21].

The clinical variables that were associated with BMD were age, age group, and BMI. Although studies have shown an association between BM and the use of ATV[9,20,21] such as duration and class, this association was not evidenced in this study. PI was used with most participants, which limited the analysis of its effect on BM. BMD showed a negative correlation with age, as observed recently[20,22]. Pubertal delay and disease chronicity justify this association. Adolescents with HIV initiate puberty later, delaying the accelerated BM gain characteristic of puberty[24]; and older participants have a longer period of exposure to the disease and, therefore, are more exposed to the deleterious effects of the disease. Longitudinal data show that adolescents with vertical HIV have lower BM acquisition during puberty compared to HIV-negative adolescents[4]. Participants with reduced BMD were thinner and older, a difference that was maintained after adjustment for height. Low weight, more prevalent in children and adolescents with vertical HIV, is associated with lower BMD and related to disease chronicity[20-22]. The compromised nutritional status and the chronicity of the disease seem to negatively impact the acquisition of BM in children and adolescents with vertical HIV.

The pathophysiology of bone loss in children and adolescents with HIV is complex and multifactorial. Different mechanisms seem to act on the activity and response of bone cells depending on the clinical conditions, treatments received, and the life cycle of the affected person[8]. While some studies show an increase in bone remodeling, others show the opposite result. These studies differ in terms of the profile of the participants evaluated. Low bone remodeling is described in children under prepubertal majority, with analysis of markers of bone formation and resorption adjusted for age and sex, compared to a control group[23]. High bone remodeling is described in older, mostly pubertal participants with analyses of markers of bone formation and resorption without adjustment for sex, age, or pubertal stage[20]. Bone metabolism markers vary throughout childhood and adolescence, being highest during puberty[25]. The high bone remodeling observed in the older, mostly pubescent group, probably reflects this physiological moment. In a longitudinal evaluation, BMD increases progressively with age, but at a lower magnitude than in children and adolescents without HIV, such that by age 18, aBMD and volumetric BMD are low[20]. Considering that there is no BM loss but insufficient gain, low bone remodeling seems to be the most plausible pathophysiological mechanism. This phenomenon is observed indirectly in this study, since the adolescents had a lower BMD *Z*-score and a higher BMD g/cm^2 than the schoolchildren.

This study is the first national study and the second at the international level to demonstrate the limitation of the DXA technique in the evaluation of BMD in children and adolescents with HIV, when interpreted without adjustment for height. We recommend adjusting BMD for height in the evaluation of BM by DXA in children and adolescents with HIV to avoid the diagnostic inaccuracy inherent to this technique. In order to know more precisely the evolution of BMD assessed by DXA throughout childhood and adolescence in this clinical condition, it would be of great interest that ongoing longitudinal studies incorporate the adjustment of BMD for height in their study protocol.

The limitations of this study include data transversality, which limits the establishment of a cause-and-effect relationship; the nonprobability sample, which does not guarantee the representativeness of the population of children and adolescents with vertical HIV; and the reduced number of participants in clinical categories N and C, which limited the analysis of BMD variations between clinical categories.

CONCLUSIONS

Adjustment for height reduced the occurrence of reduced BMD and low BM in the lumbar spine of children and adolescents with vertical HIV, indicating its relevance in the evaluation of BM by DXA in order to avoid false-positive diagnoses of BM loss. Reduced BMD was associated with greater age and lower BMI.

AUTHORS' CONTRIBUTIONS

LBA, TFN: Conceptualization, Data curation, Formal analyses, Writing – original draft. **DMV:** Conceptualization, Funding acquisition, Project administration, Formal analyses, supervision, Writing – original draft, Writing – review & editing.

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