

Clinical Determinants of Bone Mineral Density (BMD) in Perinatally HIV-Infected Children

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ABSTRACT*

Background: HIV-infected children (HIV+) may be at risk for poor bone mineral accrual, but the etiological factors are ill-defined. We sought to characterize bone mineral density (BMD) among HIV+ children enrolled in the US-based PHACS Adolescent Master Protocol (AMP) and to evaluate associations with antiretroviral therapy (ART) as well as virologic and nutritional factors.

Methods: Total body (TB) and lumbar spine (LS) BMD were measured by dual energy x-ray absorptiometry (DXA) in 100 HIV-infected children (HIV+). Clinical (HIV stage and viral load, CD4 %, current ART), and anthropometric data were obtained simultaneously. Age- and sex-adjusted z-scores were calculated for height, BMI, and BMD (adjusted by bone age if outside[†] s.d. from chronological age) using population standards. Children with low BMD (TB or LS Z-score < -1.5), had Ca, PTH, bone-specific alkaline phosphatase (BSAP) and 25-OH vitamin D measurements taken. Multiple linear regression models were fit to identify predictors of LS z-scores, adjusted for race, height z, Tanner stage and HIV viral load (< 400 vs ≥ 400 copies/mL).

Results: Mean age of the cohort was 12.3 y (range 7.16–y) with 45% male. The majority was African American (76%). Compared to population norms, the cohort was shorter (Z=-3.74, P<0.0001), with greater BMI (Z=3.00, P = 0.0002) and lower TB BMD (Z = -0.220, P=0.015). LS BMD did not differ from normal (Z=0.052, P=0.568). In an adjusted analysis, children on NNRTI therapy had higher LS Z-scores (estimate 0.68, p=0.0027) and those on PI therapy had lower scores (-0.49 ±0.052). There was no association with NRTI therapy (estimate 0.55 ±0.19).

Children with viral load < 400 copies/mL had lower LS scores (estimate 0.57 ±0.003). The percent of children with z < -1.5 on SP, TB or either with low LS or TB had higher follow-up laboratory tests, 67% of which had low serum 25-OH D (< 40 ng/mL). All had normal Ca. Children with lower 25-OH D had higher PTH compared to those with normal 25-OH D (mean 44 vs 30 pg/mL, p=0.05), while there was no difference in BSAP.

Conclusion: Low BMD among HIV+ children is common. Limited data suggest vitamin D deficiency may be an important contributing factor and should continue to be evaluated. NNRTI therapy may be protective and PI detrimental to bone health.

* Data presented in abstract based on data available by August 16th, 2008

BACKGROUND

Low bone mass has been previously observed in perinatally HIV-infected children and youth. However, the etiology is poorly understood and the long-term consequences are unknown (1-4).

Adolescence is a critical period of bone mineral accretion, as peak bone mass is achieved by age 30, and approximately 80% of that is attained by age 18. Low peak bone mass increases the risk of osteoporosis later in life.

HIV-infected children have several risk factors for low bone mass such as delayed growth and pubertal development, low lean body mass, chronic inflammation, hormonal dysregulation, vitamin D deficiency, malabsorption and physical inactivity (5-8).

The impact of specific antiretroviral therapies (ART), viral load and vitamin D deficiency on bone mass during adolescence is not clear.

OBJECTIVES

We sought to quantify bone mineral density (BMD) among HIV+ children enrolled in the US-based PHACS Adolescent Master Protocol (AMP) and to evaluate associations with pubertal development and ART as well as virologic and nutritional factors.

METHODS*

Study Design

Protocol: The Adolescent Master Protocol (AMP), which is part of Pediatric HIV/AIDS Cohort Study (PHACS), is a prospective cohort study conducted at 12 US sites designed to define the impact of HIV infection and ART on pre-adolescents and adolescents with perinatal HIV infection (HIV+). A group of HIV-uninfected (HIV-) but perinatally HIV-exposed children with similar sociodemographic backgrounds and age distribution has been enrolled for comparison. Domains to be investigated include growth and sexual maturation, metabolic risk factors for cardiovascular disease, cardiac, function, bone health, neurological, neurodevelopmental, language, hearing and behavioral function, and human papillomavirus (HPV) infection. Children from 7 years of age until their 16th birthday born to HIV-infected mothers are eligible for enrollment into AMP.

Enrollment: Enrollment began in March 2007. As of December 16, 2008, there were 319 HIV+ and 101 HIV- neg enrolled in AMP. *This report includes baseline data on 249 HIV+ who underwent dual energy x-ray absorptiometry (DXA) scans.*

DXA and BMD (Bone Mineral Density) Trigger

One DXA scan per participant to measure total body BMD (TBBMD) and lumbar spine BMD (LSBMD). Measurements were standardized at the Tufts Body Composition Center.

Age-gender BMD Z-scores calculated from population standards. **Age was based on bone age if chronological age was outside 1 standard deviation (s.d.) of bone age.**

Definition of children who met BMD Trigger: LSBMD Z-score < -1.5 or TBBMD Z-score < -1.5.

Follow-up on children who met BMD Trigger: Serum calcium (Ca), thyroid stimulating hormone (TSH), parathyroid hormone (PTH), bone specific alkaline phosphatase (BSAP) and 25-OH vitamin D (25-OH D). (Results on all children.)

Clinical and anthropometric data

CDC classification, HIV viral load (copies/mL), CD4 count (cells/mm³), current antiretroviral use, Z-scores for height, weight and BMI, Tanner staging and radiograph to determine bone age collected at same visit as DXA scan.

Statistical Methods

Differences between groups tested by Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables with missing excluded. Multivariate general linear model used to determine significant independent predictors of LSBMD Z-score.

* Data presented in poster based on data available by December 16th, 2008

RESULTS

Table 1: Sociodemographic and Nutritional Characteristics by BMD Trigger Status

Characteristic	Met BMD Trigger		p-value
	No (N=200)	Yes (N=49)	
Age (yr)	Median (Q1, Q3) 12.85 (10.75, 14.41)	12.09 (10.82, 13.98)	0.310*
Race/ethnicity [†]	Hispanic 33 (77%) Black 154 (83%) White/other 8 (12%) Unknown 1 (100%)	10 (23%) 31 (77%) 0 (0%) 0 (0%)	0.044**
Sex	Male 85 (75%) Female 115 (85%)	29 (25%) 20 (15%)	0.039**
Height Z-score	Median (Q1, Q3) -0.15 (-0.93, 0.38)	+1.38 (-2.02, -0.55)	<.001**
Tanner Stage Categories	1-2 77 (72%) 3-4 86 (86%)	30 (28%) 14 (14%)	0.009**
Missing	5 (71%)	2 (29%)	

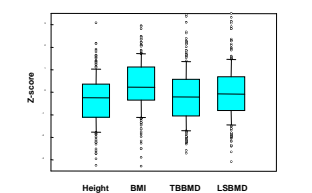
*Kruskal-Wallis Test **Fisher's Exact Test † Black + Non-Hispanic Black; White/other=Non-Hispanic White/other

RESULTS

Table 2: Disease Severity and ART by BMD Trigger Status

Characteristic	Met BMD Trigger		p-value (Fisher's exact test)
	No (N=200)	Yes (N=49)	
CDC Category	N/A B 80 (39%) C 54 (74%) Missing 12 (8%)	17 (18%) 16 (23%) 13 (19%) 3 (2%)	0.68†
CDC Percent	< 15% 15 (20%) > 2% 142 (79%) Missing 6 (7%)	0 (0%) 9 (19%) 38 (21%)	0.170
HIV-RNA (copies/mL)	0-400 124 (78%) 401-5000 27 (8%) 5001-50000 21 (8%) 50001+ 11 (7%) Missing 5 (8%)	35 (22%) 5 (12%) 5 (11%) 1 (1%)	0.53†
Current PI use	No 49 (82%) Yes 146 (81%) Missing 5 (8%)	11 (89%) 35 (19%) 3 (38%)	1.000
Current NNRTI use	No 142 (79%) Yes 53 (87%) Missing 5 (8%)	38 (21%) 8 (13%) 3 (38%)	0.192
Current NRTI use	No 12 (71%) Yes 183 (82%) Missing 5 (8%)	5 (29%) 41 (18%) 3 (38%)	0.332

Figure 1: Height, BMI, TBBMD and LSBMD Z-scores in HIV+ Children (n=249)



Compared to population norms, the cohort was shorter (Z=-2.74, P<0.0001), and had greater BMI (Z=3.00, P < 0.0001). TBBMD (Z=-0.210, P=0.010) was lower than normal and LSBMD did not differ from normal (Z=-0.080, P=0.43), both accounting for bone age (See Methods BMD Z-scores).

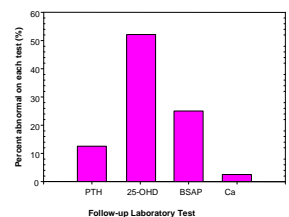
Met BMD Trigger (TBBMD or LSBMD Z-score < -1.5)
19.7%
TBBMD Z-score < -1.5 15.8%
LSBMD Z-score < -1.5 9.6%

Table 3: Follow-up Test Results by 25-OH Vitamin D Status Among HIV+ Who Met BMD Trigger (n=41)

Serum Measurement	Low 25-OH Vitamin D (< 20 ng/mL)		
	No (N=21)	Yes (N=20)	p-value
Thyroid Stimulating Hormone (mIU/L)	Median (IQR, 75 th) 1.18 (0.75, 1.92)	1.3 (0.79, 2.23)	0.823**
Parathyroid Hormone (pg/mL)	Median (IQR, 75 th) 44.1, 57.0	29.5 (20.0, 38.0)	0.024***
Calcium (mg/dL)	9.5, 9.7 (9.3, 9.7)	9.7 (9.4, 10.0)	0.116**
Bone Specific Alkaline Phosphatase (Percent Annual Increase)	% 25.0	26.3	1.00*

*Fisher's Exact Test ** Wilcoxon Test † Abnormal levels determined by age

Figure 2: Prevalence of Abnormal Laboratory Results among HIV+ Children Who Met BMD Trigger (n=41)



Among HIV+ children with low BMD, approximately half (52.5%) have low levels of 25-OH vitamin D.

Table 4: Determinants of LSBMD Z-score in 233 HIV+ Children – Multivariate Model[†]

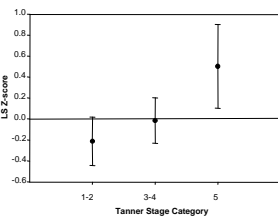
Characteristic	Estimate	Standard Error	p-value
Male vs. female	0.0713	0.137	0.603
Race/ethnicity [†]			
Hispanic vs. Black	-0.219	0.185	0.237
White/other vs. Black	-0.480	0.261	0.068
Height Z-score	0.403	0.059	<.0001
Tanner Stage Categories			
Tanner 3-4 vs. Tanner 1	0.117	0.148	0.428
Tanner 5-6 vs. Tanner 1	0.651	0.206	0.002
Current PI use (yes vs. no)	-0.311	0.213	0.147
Current NNRTI use (yes vs. no)	0.429	0.188	0.024
Current NRTI use (yes vs. no)	0.477	0.348	0.171
HIV RNA >400 vs. <400 copies/mL	0.367	0.154	0.018

*Adjusted for DXA scanner. Model includes all HIV+ with complete data on all variables (n=233)

† Black + Non-Hispanic Black; White/other=Non-Hispanic White/other

LSBMD Z-scores were positively associated with greater height Z-score, Tanner stage 5 vs. 1, NNRTI use and un-suppressed HIV viral load in multivariate analysis. Male sex, race/ethnicity, PI and NRTI use were not associated with LSBMD Z-scores.

Figure 3: LSBMD Z-scores by Tanner stage Mean (95% CI) – Unadjusted



SUMMARY AND CONCLUSIONS

Low BMD is common among HIV+ children (~ 20%).

Available data suggest vitamin D deficiency may be an important contributing factor and should continue to be evaluated.

HIV+ children may have the greatest increases in LSBMD toward the end of pubertal development ie. Tanner 5 (accounting for bone age).

NNRTI therapy may be protective to bone health.

A better understanding of factors leading to low bone mass during this important period of bone mineral accrual could lead to targeted interventions and/or changes in HIV therapy.

REFERENCES

- Apaldi SM, Horlick M, Thornton J, Cuff PA, Wang J, Kotler DP. Bone mineral content is lower in perinatally HIV-infected children. *J Acquir Immune Defic Syndr*. 2002;29:450-454.
- O'Brien KO, Razzivi M, Henderson RA, Caballero B, Ellis KJ. Bone mineral content in girls perinatally infected with HIV. *Am J Clin Nutr*. 2001;73:821-826.
- Mora S, Zamproni I, Beccio S, Bianchi R, Giacomini V, Vignano A. Longitudinal changes of bone mineral density and metabolism in antiretroviral-treated human immunodeficiency virus-infected children. *J Clin Endocrinol Metab*. 2004;89:24-28.
- Jacobson DL, Spiegelman D, Duggan C, et al. Predictors of bone mineral density in human immunodeficiency virus-1 infected children. *J Pediatr Gastroenterol Nutr*. 2005;41:339-346.
- Miller TL, Evans SJ, Orav EJ, McIntosh K, Winter H.S. Growth and body composition in children infected with the human immunodeficiency virus-1. *Am J Clin Nutr*. 1993;57:588-592.
- Chantry CJ, Byrd RS, Englund JA, Baker CJ, McKinney RE. Pediatric AIDS Clinical Trials Group Protocol 152 Study Team. Growth, survival and viral load in symptomatic childhood human immunodeficiency virus infection. *Pediatr Infect Dis J*. 2003;22:1033-1038.
- Buchacz K, Cervic JS, Lindsey JC, et al. Impact of protease inhibitor-containing combination antiretroviral therapies on height and weight growth in HIV-infected children. *Pediatrics*. 2001;108:1-7.
- Amorosa V, Tebas P. Bone disease and HIV infection. *Clin Infect Dis*. 2006;42:106-114.

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