Association of Adipokines with Bone Mineral Density in HIV+ and HIV- Women

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Abstract

Background: HIV infection is associated with low bone mineral density (BMD) and alterations in adipose-derived hormones (adipokines) such as leptin and adiponectin. Studies in the general population suggest that adipokines may be important mediators of the relationship between fat and bone, however their relationship to BMD in HIV+ populations is unknown.

Methods: BMD of the lumbar spine (LS), total hip (TH), and femoral neck (FN) were measured by dual energy X-ray absorptiometry (DXA) at baseline and over 5 years in 440 participants (318 HIV+, 122 HIV-) enrolled in the Metabolic Substudy of the Women's Interagency HIV Study. Serum leptin and adiponectin were assayed on stored sera. Multivariable linear mixed models were used to assess the effects of adipokines and HIV status on BMD over 5 years, adjusting for demographic, behavioral, and body composition and metabolic factors, and menopausal status. Models restricted to HIV+ women also adjusted for CD4, HIV RNA, and HAART use.

Results: Compared with HIV- women, HIV+ women were older (mean 44 vs. 37 years) and more likely to be postmenopausal (26% vs. 3%). HIV+ women had lower BMI (27kg/m^2 vs. 30kg/m^2), and lower leptin (18ng/mL vs. 28ng/mL) but higher adiponectin (9.4µg/mL vs. 6.4µg/mL) levels at the baseline visit. In unadjusted analysis, HIV+ women had lower LS, TH, and FN BMD than HIV- women. After adjustment for demographic, behavioral, body composition and metabolic factors, HIV+ status was associated with lower BMD at the LS (-0.077 g/cm^2), TH, (-0.047 g/cm^2), and FN (-0.048 g/cm^2) (all p<.05). There was little change in the effects of HIV on BMD after additional adjustment for adiponectin levels; HIV remained associated with lower BMD at the LS (-0.078 g/cm^2), TH (-0.044 g/cm^2), and FN (-0.051 g/cm^2) and (all p<0.01). Similar findings were observed after additional adjustment for leptin. Among HIV+ women, in unadjusted analyses, adiponectin was associated with lower TH BMD (-0.025 g/cm^2 per 10-fold adiponectin increase, p=0.04), whereas leptin was associated with higher BMD at FN (+0.027 g/cm^2 per 10-fold leptin increase, p=0.005) and TH (+0.019 g/cm^2, p=0.03). After multivariable adjustment, neither adiponectin nor leptin were associated with BMD at any site (all p>0.2).

Conclusions: HIV infection is associated with lower LS,TH, and FN BMD among women. Serum leptin and adiponectin levels do not appear to mediate the association of HIV infection with loss of BMD, and appear to have little association with BMD among HIV infected women.

Introduction

- Regional changes in fat distribution may be a strong component of bone health, particularly among HIV-infected women
- We previously demonstrated that total fat and lean mass are strong and independent predictors of hip and femoral neck bone mineral density (BMD), and that greater trunk fat was associated with increased hip and femoral neck BMD in both HIV infected and uninfected participants in the Women's Interagency HIV Study (WIHS)
- Levels of bone-active factors from adipocytes (adipokines) such as adiponectin and leptin, may mediate the relationship between adiposity ,HIV status and BMD

Methods

Study Population

- The Women's Interagency HIV Study (WIHS) is a multicenter prospective cohort study established in 1994 to investigate the progression of HIV in women with and at risk for HIV.
- 440 WIHS women enrolled in a prospective Metabolic Substudy between 2003 and 2005 from 3 WIHS sites (San Francisco, Bronx and Chicago) were included in the analysis.
- Enrollment criteria into the Metabolic Substudy included: age <65 years old, weight <264 pounds, height < 6'1", not pregnant or breast feeding currently or in past six months, and not reporting type I diabetes, use of corticosteroids, drugs used to treat osteoporosis, growth hormone, or exogenous hormones including hormonal contraceptives in the prior 12 months.
- Women underwent DXA to measure bone mineral density (BMD) and body composition at baseline and 2 and 5 years after baseline.

Measurements

Primary Predictors

Serum adiponectin (µg/mL) and leptin (ng/mL)

Secondary Predictors

HIV status, **demographic** (age at index visit, race/ethnicity, study center and enrollment cohort); behavioral (cigarette use, alcohol use, and opiate use); **body composition** (trunk and leg fat measured by DXA, fat free mass (FFM), total body fat (TBF), and percent body fat (PBF) measured by bioimpedance analysis); **anthropometric** measures (body mass index (BMI), waist circumference, Waist to Hip Ratio); **metabolic** (Hepatitis C virus (HCV) infection, serum testosterone, and vitamin D, Ca or multivitamin use); **bone turnover markers** (osteocalcin in ng/mL and C-telopeptide in ng/mL); **other** (menopause status at index visit).

Outcome

BMD in the lumbar spine (LS), total hip (TH), and femoral neck (FN) measured by DXA at baseline and at follow up visits 2 and 5 years later

Statistical Analysis

Multivariable linear mixed models were used to assess the associations of HIV status and adipokines with BMD over 5 years.

Results

Table 1. HIV-infected women were older, more likely to be HCV seropositive, postmenopausal and report taking calcium, vitamin D, and multivitamins. HIV-infected also had lower BMI and lower trunk and leg fat. Over half of all women were African-American.

	HIV-uninfected (N=122)		HIV-infected (N=318)	
	N	%	N	%
Age (yr) *#	37	(31-44)	43	(38-41)
Race				
African American	70	57	186	58
Hispanic	19	16	29	9
Caucasian	13	11	41	13
Other	20	16	62	19
Study				
Bronx/Manhattan	49	40	128	40
San Francisco	44	36	119	37
Chicago	29	24	71	22
Smoking status				
Never smoker	26	21	57	18
Current smoker	80	66	189	60
Past smoker	16	13	69	22
Opiate use ever at index visit	33	27	94	30
Calcium/Vitamin D/Multivitamin use	4	3	26	8
Postmenopausal status#	4	3	89	28
BMI* (kg/m²) *#	30.0	25.5-36.7	27.1	23.3-31.2
Body components*				
Trunk fat(kg) #	15.6	10.7-22.0	12.7	9.1-16.8
Leg fat(kg) #	11.9	8.4-16.0	8.7	5.6-12.7
Fat free mass (kg)	48.3	44.1-52.2	46.7	43.2-50.5
Total body fat (kg) #	28.2	19.7-43.1	23.9	16.0-33.0
HCV antibody positive#	17	14	102	32
Bone Turnover Marker levels*				
Osteocalcin (ng/mL	5.45	3.69-8.22	5.98	4.25- 9.05
C-Telopeptide (ng/mL) #	0.05	0.00, 0.12	0.08	0.03- 0.16
Adipokine levels*				
Leptin (ng/mL) #	19.77	8.99- 40.21	11.74	5.43-24.21
Adiponectin (µg/mL) #	5.61	4.03-7.41	6.24	3.63-9.98
CD4 count*#			399	262-598
HIV-RNA viral load*			575	80-6900
On ART			265	83
On HAART			179	56
On tenofovir			71	22

* Median(IQR)
** Baseline refers to the Index visit, i.e., the first visit when BMD/DXAs were measured.
# P<0.05 for Chi-square test or two sample t-test.

Table 2. Unadjusted associations of adiponectin and leptin with BMD in HIV-infected and uninfected women

Parameter	Lumbar Spine (g/cm2) Estimate (95% CI)	Femoral Neck (g/cm2) Estimate (95% CI)	Total Hip (g/cm2) Estimate (95% CI)
HIV-infected women			
Leptin (per 10-fold increase)	0.010 (-0.008, 0.028), p=0.28	0.027 (0.011, 0.043), p=0.005	0.019 (0.004, 0.034), p =0.028
Adiponectin (per 10-fold increase)	0.017 (-0.042, 0.009), p=0.22	-0.016 (-0.038, 0.007), p=0.19	-0.025 (-0.047, -0.004), p=0.035
HIV-uninfected women			
Leptin (per 10-fold increase)	0.025 (-0.018, 0.068), p=0.28	0.026 (-0.013, 0.065), p=0.22	0.044 (0.007, 0.080), p=0.037
Adiponectin (per 10-fold increase)	-0.083 (-0.178, 0.012), p=0.11	-0.076 (-0.161, 0.009), p=0.10	-0.088 (-0.168, -0.007), p=0.055

Table 3. Association of HIV infection with Bone Mineral Density in the WIHS Metabolic Study

Model	Lumbar Spine (g/cm²) Estimate (95% CI)	Femoral Neck (g/cm²) Estimate (95% CI)	Total Hip (g/cm²) Estimate (95% CI)
Unadjusted*	-0.086 (-0.120, -0.052) p<0.0001	-0.091 (-0.119, -0.062) p<0.0001	-0.090 (-0.119, -0.061) p<0.0001
Adjusted**	-0.078 (-0.122, -0.034) p=0.003	-0.051 (-0.085, -0.016) p=0.01	-0.044 (-0.078, -0.01) p=0.02
Adjusted + Leptin	-0.086 (-0.133, -0.040) p=.003	-0.050 (-0.085, -0.014) p=0.02	-0.05 (-0.086, -0.013) p=0.02
Adjusted + Adiponectin	-0.078 (-0.122, -0.034) p=0.003	-0.051 (-0.085, -0.017) p=0.01	-0.045 (-0.079, -0.011) p=0.02

*Adjusted only for year, and study site
**Adjusted for year, study site, race/ethnicity, age, menopause, BMI, fat free mass, lean leg mass, osteocalcin level and c-teloeptide level

Table 4. Factors associated with BMD in HIV-infected women with effect of adiponectin

Parameter	Lumbar Spine (g/cm²) Estimate (95%CI)	P-value	Femoral Neck (g/cm²) Estimate (95%CI)	P-value	Total Hip (g/cm²) Estimate (95%CI)	P-value
Adiponectin (per 10-fold increase)	0.004 (-0.028, 0.035)	0.84	0.001 (-0.027, 0.029)	0.96	-0.0003 (-0.025, 0.024)	0.97
Age (per decade)	-0.038 (-0.074, -0.002)	0.11	-0.052 (-0.079, -0.024)	0.022	-0.042 (-0.07, -0.014)	0.04
Postmenopausal Status	-0.055 (-0.085, -0.025)	0.022	-0.047 (-0.074, -0.021)	0.025	-0.057 (-0.08, -0.034	0.008
BMI (per 5 kg/m²)	-0.004 (-0.016, 0.007)	0.54	0.016 (0.006, 0.027)	0.040	0.022 (0.013, 0.032)	0.01
Fat Free Mass (kg)	0.005 (0.002, 0.007)	0.017	0.004 (0.002, 0.006)	0.023	0.003 (0.001, 0.005)	0.041
Osteocalcin (per doubling)	-0.004 (-0.012, 0.005)	0.43	-0.005 (-0.012, 0.003)	0.28	-0.007 (-0.013, 0.000)	0.12
C Telopeptide (per doubling)	-0.007 (-0.013, -0.002)	0.065	-0.001 (-0.006, 0.005)	0.83	-0.005 (-0.010, 0.000)	0.10

*Adjusted models control for time, WIHS study site, and race/ethnicity

Table 5. Factors associated with BMD in HIV-infected women with effect of leptin

Parameter	Lumbar Spine (g/cm²) Estimate (95%CI)	P-value	Femoral Neck (g/cm²) Estimate (95%CI)	P-value	Total Hip (g/cm²) Estimate (95%CI)	P-value
Leptin (per 10-fold increase)	0.002 (-0.018, 0.022)	0.84	0.002 (-0.016, 0.021)	0.82	-0.012(-0.028, 0.004)	0.25
Age (per decade)	-0.045 (-0.082, 0.009)	0.093	-0.055 (-0.083, -0.027)	0.029	-0.046 (-0.073, -0.018)	0.047
Postmenopausal Status	-0.048 (-0.077, -0.019)	0.049	-0.045 (-0.071, -0.019)	0.044	-0.055 (-0.077, -0.033)	0.017
BMI (per 5 kg/m²)	-0.005 (-0.018, 0.009)	0.53	0.016 (0.004, 0.028)	0.076	0.026 (0.015, 0.036)	0.017
Fat Free Mass (kg)	0.005 (0.002, 0.007)	0.029	0.004 (0.002, 0.006)	0.039	0.003 (0.001, 0.005)	0.05
Osteocalcin (per doubling)	-0.003 (-0.011, 0.004)	0.46	-0.004 (-0.011, 0.003)	0.32	-0.005 (-0.011, 0.001)	0.18
C Telopeptide (per doubling)	-0.008 (-0.013, -0.003)	0.060	-0.001 (-0.006, 0.005)	0.84	-0.006 (-0.01, -0.001)	0.085

*Adjusted models control for time, WIHS study site, and race/ethnicity

Conclusions

- HIV is associated with lower lumbar spine, total hip, and femoral Neck BMD among women
- Serum leptin and adiponectin levels do not appear to mediate the association of HIV infection with loss of BMD
- Leptin and adiponectin appear to have little association with BMD among HIV infected women after multivariable adjustment.

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