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

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Abstract

Background—HIV infection is associated with low bone mineral density (BMD) and alterations in adipokines, which may mediate the relationship between fat and bone.

Objective—To evaluate the relationship of adiponectin and leptin with BMD in HIV-infected and uninfected women.

Methods—We measured BMD over 5 years at the lumbar spine (LS), total hip (TH), and femoral neck (FN) using dual energy X-ray absorptiometry in 318 HIV-infected and 122 HIV-uninfected participants of the multicenter Women's Interagency HIV Study (WIHS). Total adiponectin and leptin were assayed on stored sera. Multivariable linear mixed models assessed the effects of adipokines and HIV status on BMD.

Results—HIV-infected women had higher adiponectin (median 6.2μg/mL vs. 5.6μg/mL,) but lower leptin (11.7ng/mL vs. 19.8ng/mL) levels at baseline (both $p<.05$) compared with HIV-uninfected women. HIV-infection was associated with lower BMD at the LS ($-0.074 g/cm^2$), FN ($-0.049 g/cm^2$), and TH ($-0.047 g/cm^2$) (all $p<.05$) after adjusting for demographic, behavioral and metabolic factors. HIV infection remained associated with lower BMD at each site, with little

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change in the effect sizes after additional adjustment for adiponectin or leptin. Among HIV-infected women, higher adiponectin was associated with *lower* TH BMD (−0.025g/cm^2 per 10-fold increase, p=0.035), whereas higher leptin was associated with *higher* BMD at FN (+0.027g/cm^2 per 10-fold increase, p=0.005) and TH (+0.019g/cm^2, p=0.028). After multivariable adjustment, the adipokines showed little association with BMD at any site (p>0.8 for adiponectin; p>0.2 for leptin).

Conclusions—Alterations in serum adiponectin and leptin do not explain low BMD in HIV-infected women.

Keywords

bone mineral density; adipokine; body composition; HIV

Introduction

Long-term consequences of HIV infection and antiretroviral therapy, particularly disturbances of bone metabolism, are emerging concerns given the growing numbers of older adults living with HIV. Regional changes in fat distribution may be an important determinant of bone health. We have demonstrated that HIV-infected women are at greater risk of lipoatrophy than are HIV-uninfected women [1, 2], and that lower total fat and lean mass are strong, independent predictors of lower hip and femoral neck bone mineral density (BMD) in both HIV-infected and uninfected women [3]. Levels of adipocyte-derived hormones (adipokines) may differ by location and type of fat depot, and may mediate the relationship between regional fat distribution and BMD [4]. Among HIV-infected persons, little is known about the relationship between adipokines and regional fat distribution or BMD. The objective of this study was to evaluate the relationship of the adipokines adiponectin and leptin with BMD in HIV-infected and uninfected women. We hypothesized that high adiponectin and low leptin would be associated with reduced BMD in HIV-infected women, and that both adiponectin and leptin would mediate the relationship between HIV status and BMD.

Methods

The WIHS is a multicenter cohort study that originally enrolled HIV-infected and HIV-uninfected women from six U.S. locations in 1994–95. Details of the study design, data collection methods, and baseline characteristics are published elsewhere [5, 6]. Briefly, semiannual visits include an interviewer-administered questionnaire, physical examination, and collection of laboratory specimens. Between 2003 and 2011, 318 HIV-infected and 122 HIV-uninfected women with similar age, ethnicity, and risk behaviors from three WIHS sites (San Francisco, Bronx and Chicago) enrolled in a 5-year Metabolic Substudy, and BMD, adiponectin, and leptin were measured. Eligibility criteria have been published previously [3]. The institutional review boards of participating institutions approved the study protocol, and all participants provided informed consent.

The primary outcome of interest was BMD at the lumbar spine (LS), femoral neck (FN), and total hip (TH) measured by DXA (GE/Lunar Prodigy, Madison, WI) at index and 2 and 5

years later. Primary predictors were total adiponectin and leptin, measured by ELISA (Millipore, Billerica, MA). Candidate covariates included **demographics**: age and race/ethnicity; **behavioral factors**: cigarette smoking (never, current, or past smoker), opiate use before index visit; **body composition**: leg and trunk fat and lean mass (measured in kg by DXA), total fat free mass (FFM), total body fat (TBF), and percent body fat (PBF, determined by bioimpedance analysis [7, 8]), and body mass index (BMI) in kg/m^2; **metabolic factors**: free testosterone level (ng/dL) at index visit, and use of calcium, vitamin D or multi-vitamins; **menopausal status** (self-reported amenorrhea ≥12 months for women ≥45 years); **bone turnover markers** osteocalcin and C-telopeptide (ng/mL) (IDTS Ltd, Fountain Hills, AZ). **HIV-related factors** included Hepatitis C virus infection (positive antibody and RNA), self-reported history of AIDS; plasma HIV-RNA level, CD4 cell count, and nadir CD4 count, current use of tenofovir and highly active antiretroviral therapy (HAART), cumulative exposure to HAART prior to index visit; and type of HAART regimen: protease inhibitor- based, non-nucleoside reverse transcriptase inhibitors- based, or other.

Baseline characteristics of HIV-infected and uninfected participants were compared with chi-squared tests for categorical variables and 2-sample t tests or Wilcoxon rank sum test for continuous variables. Associations of adipokines and HIV status with BMD over time were assessed using linear mixed models, with random intercepts and slopes using unstructured covariance. We first compared associations of the adipokines with BMD at each site, among HIV-infected and uninfected women separately, adjusted for time and study site. Multivariable models examined associations of HIV with BMD at each site, adjusting for demographic, metabolic, and body composition factors. Study site, enrollment year, age and race were forced in the models while other covariates were retained using backward selection if p value was <0.05. We tested whether inclusion of adiponectin and leptin mediated the effect of HIV on BMD at each site. Models were similarly constructed among HIV-infected women only. Because adipokines and bone turnover markers were right-skewed, they were log-transformed. Analyses were performed using SAS Version 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

A total of 440 women (318 HIV+, 122 HIV-) completed up to three DXA scans over 947 person-visits. Median time between consecutive scans was 2.6 years (2.0 years between the 1^{st} and 2^{nd} scans and 3.4 years between the 2^{nd} and 3^{rd} scans). Participant characteristics are shown in Table 1.

Associations of adiponectin and leptin with BMD in HIV-infected and uninfected women

In analyses adjusted only for time and study site, among HIV-infected women, higher adiponectin was associated with lower BMD at all three sites, although the association reached significance only for TH ($-0.025 g/cm^2$ per 10-fold adiponectin increase, p=0.035) (Table 2). By contrast, higher leptin was associated with higher BMD at all three sites, with statistically significant associations for FN ($+0.027 g/cm^2$ per 10-fold leptin increase, p=0.005) and TH ($+0.019 g/cm^2$, p=0.028). Among HIV-uninfected women, higher

adiponectin was weakly associated with lower BMD at all sites, and leptin was weakly associated with higher BMD levels at all sites; none of these associations reached statistical significance.

Association of HIV and adipokines with BMD

In analyses adjusted only for time and study site (Table 2), HIV infection was associated with lower BMD at the LS (−0.086 g/cm^2), FN (−0.091 g/cm^2), and TH (−0.090 g/cm^2), compared with HIV-uninfected women (all p<.0001). After adjustment for demographic, behavioral and metabolic risk factors, HIV infection remained associated with lower BMD at all 3 sites, but the association was attenuated by 14% in the LS (−0.074 g/cm^2) and by almost 50% in the FN (−0.049 g/cm^2) and TH (−0.047 g/cm^2); (all p≤0.02). After adjusting for adiponectin and leptin, there was little change in the effects of HIV on BMD (Table 2). We also determined whether the rate of BMD change differed by HIV status at any site. In fully adjusted analyses that included adiponectin, HIV-infected women had faster declines in BMD in the TH (−0.004 g/cm^2/yr, 95%CI: −0.007, −0.001; p=0.025) and in the LS (−0.005 g/cm^2/yr, 95%CI: −0.008, −0.001; p=0.041). HIV infection was also associated with a non-significant decline in FN BMD (−0.003 g/cm^2/yr, 95%CI: −0.007, +0.001; p=0.15).

Factors associated with BMD in HIV-infected women

After adjustment for age, race/ethnicity, menopausal status, body composition, and bone turnover markers, adiponectin showed little association with BMD at the LS (0.005 g/cm^2 per 10-fold increase, 95%CI: −0.036 to 0.045, p=0.77), FN (−0.009 g/cm^2 per 10-fold increase, 95%CI: −0.036 to 0.019, p=0.55), or TH (0.0004 g/cm^2 per 10-fold increase, 95%CI: −0.039 to 0.040, p=0.97). Similarly, leptin appeared to have little association with BMD at the LS (−0.001 g/cm^2 per 10-fold increase, 95%CI: −0.025 to 0.024, p=0.93), FN (0.015 g/cm^2 per 10-fold increase, 95%CI: −0.018 to 0.032, p=0.15), or TH (0.008 g/cm^2 per 10-fold increase, 95%CI:−0.013 to 0.029, p=0.36). Factors independently associated with lower BMD levels among HIV-infected women included postmenopausal status (all 3 sites), age (TH and FN) and reduced FFM (LS and FN).

The relationship between adiponectin and TH BMD lost statistical significance after controlling for age, race, and menopause status (−0.017 g/cm^2/yr, 95%CI: −0.039, +0.006; p=0.13). Other models controlling individually for FFM, leg lean mass, and C-telopeptide weakened associations of adiponectin with TH BMD. HIV-related factors showed little association with BMD in fully adjusted models (data not shown). Similarly, leptin was not significantly associated with BMD after the addition of body composition measures into the multivariable models, specifically adding FFM (0.014 g/cm^2/yr, 95%CI: −0.003, +0.03; p=0.14 for FN; 0.01 g/cm^2/yr, 95%CI: −0.005, +0.025; p=0.22 for TH), or TBF (0.003 g/cm^2/yr, 95%CI: −0.017, +0.023; p=0.76 for FN and −0.008 g/cm^2/yr, 95%CI: −0.025, +0.009; p=0.39 for TH) or lean leg mass (0.013 g/cm^2/yr, 95%CI: −0.002, +0.027; p=0.11 for TH).

Discussion

In this large, multicenter cohort study of HIV-infected and uninfected women, HIV infection is associated with lower LS, TH and FN BMD, independent of serum adipokine levels. Serum adiponectin and leptin levels do not appear to mediate the association of HIV infection with BMD loss, and had little association with BMD among HIV-infected women after multivariable adjustment. Body composition measures including FFM and leg lean mass attenuated the effect of adiponectin on BMD, and may mediate the relationship between HIV and bone loss. Similarly, FFM, TBF, and leg lean mass attenuated the effect of leptin on bone, suggesting that body composition may be a more important mediator of the relationship between HIV and bone loss than leptin or adiponectin.

Several cross sectional studies among HIV-uninfected populations have reported inverse associations between adiponectin and BMD [9–13], and positive associations between leptin and BMD [14–18]. In some, leptin remained associated with BMD after adjustments for fat mass and weight [14], fat mass [15] or percent body fat [16, 18]. In a large cohort study, leptin levels were associated with BMD only in women; however adjustment for fat mass eliminated this association [17]. In the National Health and Nutrition Examination Survey, leptin was no longer associated with BMD after adjusting for BMI in women, and leptin was *inversely* associated with BMD in men; controlling for leptin did not alter the relationship between BMI and BMD [19].

Few longitudinal studies have evaluated the associations between adipokines and BMD in uninfected populations. Among older women, higher adiponectin has been associated with reduction in hip BMD after adjusting for weight change [20], and with greater loss of LS BMD after adjusting for trunk:leg fat ratio [21]; others have found no association of adiponectin and 4-year bone loss [22]. Among older women, leptin has been associated with less total BMD loss adjusting for FFM, less FN BMD loss adjusting for fat mass [21], and higher BMD and lower bone turnover independently of BMI [23], but did not predict BMD change in several studies [20, 23, 24]. Taken together, the role of adiponectin in bone loss remains unclear, whereas leptin does not appear to independently predict bone loss among HIV-uninfected women after accounting for measures of adiposity.

Our findings are consistent with those reported in HIV-uninfected populations, however much less is known about the relationships between adipokines and BMD among HIV-infected populations. Published studies are limited by cross-sectional design, small sample size, inclusion of only men, and lack of multivariate analyses. Among 107 HIV-infected men in the early HAART era, greater leptin was associated with lower BMD in men with peripheral lipoatrophy after controlling for fat and lean mass, but not in those without lipoatrophy [25]. In 117 Italian HIV-infected men and women with normal BMI, leptin was *inversely* correlated with total BMD; however no multivariable analyses were performed and thus adiposity was not taken into account [26].

Ours is the first longitudinal study conducted among HIV-infected women to evaluate the relationship of leptin and adiponectin to BMD, and the largest study conducted in an HIV-infected population to date. Our study has a number of strengths. First, we performed

regional assessments of BMD at sites of clinical relevance for fracture risk, rather than total body BMD or bone mineral content. Second, we measured total and regional fat and lean mass in women with a range of BMI, although the majority of women in the cohort are overweight. Third, the WIHS comparison group of HIV-uninfected women is well-matched, with similar risk factors for bone disease, and is representative of the HIV epidemic among US women.

Our study has several limitations. We did not measure regional subcutaneous or visceral fat. Additionally, our primary outcome was BMD, rather than fracture, which would require a larger number of subjects and longer follow-up, given the age of the participants. Last, because the WIHS is comprised entirely of women, our findings may not be generalizable to HIV-infected men.

In conclusion, in this cohort of HIV-infected and uninfected women, serum leptin and adiponectin levels do not appear to mediate the association of HIV infection with BMD decline, and have little association with BMD after multivariable adjustment. Measures of body composition appear to modify the effect of adiponectin and leptin on bone, suggesting that body composition is a more important mediator of the relationship between HIV and bone loss than adipokines among women.

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Table 1

Characteristics of HIV uninfected women and HIV infected women at index visit **

	HIV-uninfected (N=122)	HIV-infected (N=318)
Age (yr), median (IQR) *	37.0 (31.0, 44.4)	43.1 (38.0, 49.2)
Race, n (%)		
African American	70 (57%)	186 (58%)
Hispanic	19 (16%)	29 (9%)
Caucasian	13 (11%)	41 (13%)
Other	20 (16%)	62 (19%)
Study center, n (%)		
Bronx/Manhattan	49 (40%)	128 (40%)
San Francisco	44 (36%)	119 (37%)
Chicago	29 (24%)	71 (22%)
Enrollment cohort, n (%) *		
Original (1994–95)	45 (37%)	211 (66%)
2nd enrollment (2001–02)	77 (63%)	107 (34%)
Smoking status, n (%)		
Never smoker	26 (21%)	57 (18%)
Past smoker	16 (13%)	69 (22%)
Current smoker	80 (66%)	189 (60%)
Opiate use ever at index visit, n (%)	33 (27%)	94 (30%)
Calcium/Vitamin D/Multivitamin use, n (%)	4 (3%)	26 (8%)
Postmenopausal status at index visit, n (%) *	4 (3%)	89 (28%)
BMI (kg/m^2), median (IQR) *	30.0 (25.5, 36.7)	27.1 (23.3, 31.2)
Body components, median (IQR)		
Trunk fat (kg) *	15.6 (10.7, 22)	12.7 (9.1, 16.8)
Leg fat (kg) *	11.9 (8.4, 16)	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) *	29.2 (19.3, 43.1)	23.9 (16.0, 33.0)
Percent body fat (%) *	39.0 (30.3, 46.3)	33.9 (26.0, 40.3)
Hepatitis C virus infection, n (%) *	17 (14%)	102 (32%)
Bone Turnover Marker levels, median (IQR)		
Osteocalcin (ng/mL)	5.45 (3.69, 8.22)	5.98 (4.25, 9.05)
C-Telopeptide (ng/mL) *	0.05 (0, 0.12)	0.08 (0.03, 0.16)
Adipokine levels		
Adiponectin (μg/mL) *	5.61 (4.03, 7.41)	6.24 (3.63, 9.98)
Leptin (ng/mL) *	19.77 (8.99, 40.21)	11.74 (5.43, 24.21)

	HIV-uninfected (N=122)	HIV-infected (N=318)
AIDS diagnosis, n (%)	-	146 (46%)
CD4 count (cells/ml), median (IQR) *	-	399 (262, 598)
CD4 nadir (cells/ml), median (IQR) *	-	248 (128, 353)
HIV RNA viral load, median (IQR)	-	575 (80, 6900)
On ART, n (%)	-	265 (83%)
On HAART, n (%)	-	179 (56%)
On tenofovir, n (%)	-	71 (22)
Cumulative HAART exposure (mo), median (IQR)	-	48 (30, 72)
Type of HAART, n (%)		
PI only	-	85 (47%)
NNRTI only	-	66 (37%)
dual/other	-	29 (16%)

*P<0.05 for Chi-squared test, two sample t-test (for age) or Wilcoxon rank-sum test (for other continuous variables that are not normally distributed)

**Index visit refers to the first visit when BMD/DXAs were measured.

#Abbreviations: HIV: human immunodeficiency virus; BMI: body mass index; ART: antiretroviral therapy; HAART: highly active antiretroviral therapy; PI: protease inhibitor; NNRTI: non-nucleoside analog reverse transcriptase inhibitor

Table 2

Association of adiponectin, leptin, and HIV infection with Bone Mineral Density in the WIHS Metabolic Study

Model	Lumbar Spine (g/cm^2) Estimate (95% CI)	Femoral Neck (g/cm^2) Estimate (95% CI)	Total Hip (g/cm^2) Estimate (95% CI)
HIV-infected women			
Adiponectin (per 10-fold increase) *	−0.017 (−0.044, 0.011), p=0.22	−0.016 (−0.040, 0.009), p=0.19	−0.025 (−0.049, −0.002), p=0.035
Leptin (per 10-fold increase) *	0.010 (−0.009, 0.029), p=0.28	0.027 (0.009, 0.044), p=0.005	0.019 (0.002, 0.036), p =0.028
HIV-uninfected women			
Adiponectin (per 10-fold increase) *	−0.053 (−0.164, 0.059), p=0.32	−0.045 (−0.147, 0.056), p=0.35	−0.062 (−0.156, 0.032), p=0.18
Leptin (per 10-fold increase) *	0.020 (−0.031, 0.071), p=0.42	0.020 (−0.027, 0.066), p=0.37	0.039 (−0.004, 0.082), p=0.070
HIV+ vs. HIV−:			
Simple *	−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 **	−0.074 (−0.122, −0.030) p=0.003	−0.049 (−0.087, −0.011) p=0.01	−0.047 (−0.084, −0.010) p=0.02
Adjusted + Adiponectin	−0.076 (−0.122, −0.030) p=0.003	−0.049 (−0.088, −0.011) p=0.01	−0.048 (−0.086, −0.010) p=0.02
Adjusted + Leptin	−0.085 (−0.135, −0.036) p=0.002	−0.049 (−0.088, −0.009) p=0.02	−0.054 (−0.094, −0.014) p=0.02

* Adjusted for time and study site

** Adjusted for time, study site, race/ethnicity, age, menopause, fat free mass, lean leg mass, osteocalcin level and c-telopeptide level