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Decreased bone mineral density and increased fracture risk in aging men with or at risk for HIV infection

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Abstract

Background—Osteopenia has been described in HIV-infected persons, but most studies have not focused on aging men, have not included an HIV-negative comparison group with similar risks to those of the HIV-infected men, or lacked data on fracture rates.

Methods—We analyzed bone mineral density (BMD) and incident fractures in 559 men who were ≥ 49 years old with or at-risk for HIV, including 328 with and 231 without HIV infection.

Results—Median age was 55 years, 56% were black and 89% had used illicit drugs. In unadjusted analysis, BMD was lower in HIV-infected compared with HIV-uninfected men at the femoral neck (0.97 ± 0.14 versus 1.00 ± 0.15 g/cm^2; $P < 0.05$) and lumbar spine (1.17 ± 0.20 versus 1.20 ± 0.21 g/cm^2; $P = 0.06$); both differences were significant ($P < 0.05$) after adjusting for age, weight, race, testosterone level, and prednisone and illicit drug use. Non-black race and body weight were independently associated with BMD at both measurement sites and methadone therapy was independently associated with spine BMD. Among HIV-infected men, 87% had taken antiretrovirals and 74% had taken protease inhibitors, but their use was not associated with BMD. Among men who had at least one subsequent study visit (94%), incident fracture rates per 100 person-years differed among men with normal BMD, osteopenia and osteoporosis (1.4 versus 3.6 versus 6.5; $P < 0.01$). A 38% increase in fracture rate among HIV-infected men was not statistically significant.

Conclusions—HIV infection is independently associated with modestly reduced BMD in aging men, and decreased BMD is associated with increased fracture risk.

Keywords

osteopenia; osteoporosis; bone mineral density; bone fractures; antiretroviral therapy; opiate dependence

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Introduction

Broad use of highly active antiretroviral therapy (HAART) has decreased HIV-associated mortality, but because mortality is declining while incidence is remaining stable, a greater number of older adults are living with HIV infection. These trends suggest that increasing numbers of persons with HIV will experience the sequelae of aging, including osteoporosis and fractures.

Osteoporotic fractures are associated with significant morbidity. Whereas bone mass is largely genetically determined, certain life-style and hormonal factors that are prevalent among HIV-infected persons are associated with low peak bone mass and disordered bone metabolism [1, 2]. These include physical inactivity [3], decreased intake of calcium and vitamin D [4], cigarette smoking [5–7], alcohol use, depression [8–10], opiate use [11] and low testosterone levels [12,13]. Increased levels of pro-inflammatory cytokines associated with HIV infection, including interleukin-1, interleukin-6 and tumor necrosis factor, may also contribute directly to accelerated bone loss [14].

Several studies have reported an increased prevalence of reduced bone mineral density (BMD) among HIV-infected persons [14–21]. Although an association between reduced BMD and protease inhibitor therapy has been suggested [20], a number of studies have not confirmed this association [17,19,20,22–26] or have suggested that other antiretrovirals such as tenofovir may be important etiologic agents [27]. Other risk factors for osteoporosis, such as low body weight, physical inactivity, cigarette smoking and opiate use, may be particularly prevalent in HIV-infected persons [26]. HIV infection may also affect lean body mass [28], which may alter the effects of body composition on BMD [29]. To date, most studies of bone density in HIV-infected men have focused on younger men, have lacked an HIV-negative comparison group with similar drug-using and other behaviors to those of HIV-infected men, or have lacked follow-up data to assess incident osteoporotic fractures.

The objective of this study was to determine the associations of HIV infection, HAART and other lifestyle factors, with BMD and incident bone fractures in a cohort of aging men with or at risk for HIV infection.

Methods

Study participants

We studied BMD in 559 participants from the Cohort of HIV at-risk Aging Men's Prospective Study (CHAMPS), an ongoing longitudinal study of selected medical outcomes in men at least 49 years old with or at risk for HIV. Participant recruitment and study design have been described previously [30]. In brief, between August 2002 and December 2003 community-dwelling men aged 49 or older who either had documented HIV infection or were at risk for HIV through injection drug use or high-risk sexual behavior were enrolled in this prospective cohort study. Participants attended semi-annual research visits, which included a standardized interview, blood collection for HIV serology, T-lymphocyte subsets, serum testosterone levels, and weight and height measurements. The CHAMPS study was approved by the Institutional Review Boards of Montefiore Medical Center and Albert Einstein College of Medicine, and all participants provided written informed consent.

Interview data

Interview data included sociodemographic characteristics, medical history including fractures, antiretroviral and other medication use, exercise habits, drug (tobacco, heroin and cocaine) and alcohol use and substance abuse treatment. For antiretroviral therapy use, we collected self-reported data about the total duration of any antiretroviral use, and about the total duration of

protease inhibitor use. Regular exercise was defined as moderate or strenuous exercise for at least 20 min on one or more days per week.

Bone mineral density

The BMD of the femoral neck, lumbar spine (L2–L4) and total body were measured by dual X-ray absorptiometry (DEXA) using a GE Lunar Prodigy densitometer with version 6.8 software (Madison, Wisconsin, USA). The DEXA scans were performed a median of 3 days (range, 0−18 days) after the baseline interview. Osteopenia was defined as a T-score >1.0 SD and ≤2.5 SD below the average peak bone mass in young adult men, and osteoporosis was defined as a T-score >2.50 SD below the young adult mean.

Incident fractures

Men who had at least one interview following their DEXA scan during the period 2002−2006 were included in our analysis of fracture risk. Time to first incident fracture was censored at loss to follow up or final study visit. Fracture incidence rates were calculated per 100 person-years of follow-up and the factors associated with the occurrence of fractures were analyzed.

Data analysis

Associations of BMD at the femoral neck and lumbar spine with sociodemographic characteristics, drug and alcohol use, and clinical variables, including HIV serostatus and HAART use, were determined using Student's *t*-tests and Pearson's correlation coefficients for normally distributed data. *P*-values were corrected for multiple comparisons using the Bonferroni method. Factors independently associated with BMD were assessed using linear regression models, including in the model all factors with $P<0.2$ in univariate analysis. Separate regression models were constructed for the whole study population and for the HIV-infected men only. As there were unequal proportions of lean/normal weight men in the HIV-infected and uninfected groups, we constructed additional multivariate linear regression models stratified by body mass index (BMI) as lean/normal versus overweight/obese. Multivariate Cox proportional hazards models were used to determine independent risk factors for incident fractures.

Results

Study participants

The characteristics of the participant are listed in Table 1. Of the 559 participants, 59% were HIV-infected. In comparison with HIV-uninfected men, the HIV-infected men were younger, more likely to be unemployed, and less likely to be current smokers, to have hypertension, or to be overweight or obese. The HIV-infected men were also less likely to have recently used heroin or cocaine, or to be treated with methadone. Among HIV-infected men, 53% had been diagnosed with HIV infection more than 10 years previously and 87% were antiretroviral experienced.

Known risk factors for low BMD were common among both HIV-infected and HIV-uninfected men; 90% were current or former cigarette smokers, 47% were in a methadone program, 30% had used heroin in the past 5 years, 52% exercised less than once per week and 54% had serum testosterone levels <300 ng/dl. Low body weight was uncommon, with 59% of participants having BMI in the overweight or obese range ($\geq$25 kg/m^2). Among HIV-infected men, however, nearly one-half were in the lean/normal range (<25 kg/m^2). In unadjusted analyses, HIV-infected men had lower BMD and T-scores at both the femoral neck ($P = 0.05$) and lumbar spine ($P = 0.06$) than men without HIV infection (Table 1).

Factors associated with low bone mineral density

Factors associated in univariate analysis with lower BMD at both the femoral neck and lumbar spine were non-black (white or Hispanic) race ($P<0.001$), lower body weight ($P<0.0001$) and low testosterone ($P<0.05$ for the femoral neck and $P<0.0001$ for the lumbar spine). HIV infection was associated ($P<0.05$) with lower BMD at the femoral neck, and marginally associated ($P<0.06$) at the lumbar spine. Heroin use ($P=0.01$), current methadone maintenance treatment ($P<0.001$) and ever use of prednisone ($P=0.01$) were associated with lower BMD at the lumbar spine only, and older age ($P<0.0001$) and pack-years of cigarette smoking ($P=0.03$) were associated at the femoral neck only. Current or former cigarette smoking, which were both highly prevalent in this cohort, were not associated with BMD at either site.

Independent associations with lower BMD are shown in Table 2. At both of the measurement sites, non-black race, lower body weight, HIV infection and low testosterone were associated with lower BMD. Older age was associated at the femoral neck only, and current methadone maintenance treatment was associated at the lumbar spine only.

Among HIV-infected men, lower BMD was associated with non-black race, lower body weight, low testosterone (at the lumbar spine only) and longer duration of HIV infection (at the lumbar spine only), but not with lower CD4 cell counts or duration of antiretroviral therapy or protease inhibitor use (Table 3). Substituting ever use of antiretroviral drugs or protease inhibitors for duration of therapy did not significantly alter these results.

Prevalence of osteopenia or osteoporosis

Among 559 participants, 299 (54%) had osteopenia or osteoporosis including 222 (40%) with osteopenia and 77 (14%) with osteoporosis. A higher prevalence of osteopenia or osteoporosis among HIV-infected men than HIV-uninfected men was not statistically significant (55 versus 51%; $P=0.4$).

Weight-stratified analysis

As body weight was strongly associated with BMD and there were unequal proportions of lean/normal weight men in the HIV-infected and uninfected groups, we calculated the prevalence of osteopenia or osteoporosis in lean/normal weight and overweight/obese men separately; 139 lean/normal weight men (61%) and 160 overweight/obese men (48%) had osteopenia or osteoporosis of the femoral neck or lumbar spine. We then constructed unique models for the femoral neck and lumbar spine for each of these two BMI strata, including the same variables as in the combined models. Among lean/normal weight men, factors independently associated with osteopenia or osteoporosis of the femoral neck were age ($\beta=0.004$ per year; $P=0.03$), non-Black race ($\beta=0.06$; $P<0.01$), weight ($\beta=-0.004$ per kg; $P<0.001$) and HIV infection ($\beta=0.04$; $P=0.03$). Factors independently associated with osteopenia or osteoporosis of the lumbar spine were only non-black race ($\beta=0.09$; $P<0.001$) and weight ($\beta=-0.008$ per kg; $P<0.0001$).

In contrast, in the models including only overweight/obese men, HIV infection was not associated with osteopenia or osteoporosis at either site. Among overweight/obese men, factors independently associated with femoral neck osteopenia or osteoporosis were age ($\beta=0.004$ per year; $P=0.02$), non-Black race ($\beta=0.08$; $P<0.0001$), weight and low testosterone ($\beta=-0.002$ per kg; $P<0.0001$) and low testosterone ($\beta=0.05$; $P<0.01$) and factors independently associated with lumbar spine osteopenia or osteoporosis were non-black race ($\beta=0.06$; $P=0.02$), low testosterone level ($\beta=0.06$; $P<0.01$) and ever use of prednisone ($\beta=0.11$; $P=0.05$).

Fracture incidence

A total of 317 (97%) HIV-infected men and 209 (90%) HIV-uninfected men had at least one interview following their DEXA scan during 1140 person-years of follow-up. Among HIV-

infected men, there were 21 incident fractures during 686 person-years of follow-up (3.1/100 person-years), compared with 12 incident fractures during 453 person-years of follow-up among HIV-uninfected men (2.6/100 person-years; P=0.69). Fracture incidence rates per 100 person-years were 1.4 for men with normal BMD, 3.6 for men with osteopenia and 6.5 for men with osteoporosis (P<0.01).

Factors associated with incident fractures are shown in Table 4. After adjusting for age, BMI, HIV infection and presence of osteopenia or osteoporosis on baseline DEXA, black men were significantly less likely to report a fracture than non-black men. Although there was an increased hazard of 38% for HIV-infected men, this did not represent a statistically significant increase in fracture risk. Men with osteopenia or osteoporosis had nearly triple the risk for fracture compared with men with normal BMD. Replacing low BMD in the model by osteopenia and osteoporosis as separate variables, there was a progressively increasing hazard ratio with more severe BMD loss. In comparison with men with normal BMD, the adjusted hazard ratio was 2.6 (95% confidence interval, 0.99−6.7; P=0.05) for men with osteopenia and 4.0 (95% confidence interval, 1.3−11.9; P=0.01) for men with osteoporosis.

Discussion

A majority of the men in their sixth decade of life had low bone mineral density, with lower levels among HIV-infected men than uninfected men with similar risk behaviors. After adjustment for other risk factors, the effect of HIV infection was statistically significant but modest. HIV infection also increased fracture risk by approximately one-third, but this finding was not significant. It is not clear whether an effect of HIV infection on BMD might become more pronounced as men reach even older ages, or whether the increased risk of fracture due to HIV would be significant with longer follow-up or a larger sample size.

Neither any antiretroviral therapy nor protease inhibitor therapy were associated with BMD among HIV-infected men. Other factors independently associated with BMD (older age, non-black race, lower body weight and low testosterone) are generally well-known risk factors for osteopenia. The prevalence of osteopenia and osteoporosis in this cohort was slightly higher among HIV-infected than uninfected men (55 versus 51%), but similar to national estimates among white men aged 50 years and older [31]. However, the proportion of men with osteoporosis was substantially higher in this study (14%; 95% confidence interval 0.11−0.17) than in the general population. Previous studies among mostly younger male and female patients with HIV disease have estimated the prevalence of low BMD at 39 to 76% (33 to 65% with osteopenia and 6 to 16% with osteoporosis), [16,17,19,21,32] consistent with our findings among older HIV-infected and uninfected men.

Previous studies of BMD in HIV-infected cohorts have included primarily subjects with lean or normal body mass [15,17,19,21]. In this study, among the 52% of HIV-infected and 70% of HIV-uninfected men who were overweight or obese, HIV infection was not associated with BMD. This suggests that increased BMI, previously associated with slower HIV disease progression [33,34], may also lessen the effect of HIV infection on BMD. As the association between HIV infection and BMD was much stronger in lean/normal weight than overweight/obese men, it further suggests that this association is not confounded by low body weight among the HIV-infected men.

Our findings also highlight the important problem of obesity among HIV-infected and drug-using men. Although HIV infection pre-HAART was characterized by wasting, advances in treatment may now be contributing to increasing obesity among HIV-infected persons in this country. Excess weight may be desirable for some HIV-infected men, suggesting a healthy immune system. Obesity may also mask opiate or cocaine addiction, which are frequently

associated with weight loss. Among obese HIV-infected and drug-using men, weight loss may not be a priority for patients or their health care providers.

The independent association between HIV infection and BMD suggests that HIV may exert a direct effect on bone metabolism. Hormones, cytokines and body composition contribute to low BMD in HIV-infected women and men [15–17,19,21] Hypogonadally-mediated alterations of bone metabolism may lead to increased bone resorption, while pro-inflammatory cytokines (e.g. interleukin-1, interleukin-6, tumor necrosis factor) act to increase bone resorption and decrease bone formation. We did not assess biochemical markers of bone turnover or cytokines to explain mechanistically how HIV infection might adversely affect BMD. Previous smaller cross-sectional studies have noted an association between increased visceral adiposity and reduced bone density, independent of BMI [15,25], but prospective studies are needed to better describe the relationship between HIV-associated changes in body composition and BMD.

An independent association of current methadone therapy with reduced BMD of the lumbar spine in men has not previously been reported. Opiate use has been associated with central hypogonadism, leading to low BMD through reduced levels of circulating luteinizing hormone, estrogen and testosterone [11]. However, studies demonstrating this association have been small and not controlled for confounding variables, such as body weight and comorbid illness. Further research is needed to determine whether HIV-infected men on methadone are at particular risk for osteopenia or osteoporosis.

The advantages of this study include the large and ethnically diverse cohort, enrollment of aging men, an HIV-negative comparison group with similar risk behaviors to those of HIV-infected men and follow-up for incident fractures. Smaller studies enrolling primarily younger men also demonstrate low BMD, but have not recruited simultaneous controls with similar drug-use behaviors. Our study, because it included both HIV-infected and HIV-uninfected men with similar risk behaviors, permitted identification of HIV infection as a risk factor for low BMD after controlling for lifestyle variables.

The study limitations include a cross-sectional design, which precludes the assessment of causal relationships between BMD, HIV infection and opiate use. The absence of biochemical or cytokine levels also precludes conclusions about the mechanism underlying observed associations. Abdominal visceral fat was not measured to determine its relationship to BMD. Finally, although HIV infection was associated with a 38% increase in fracture rate after adjustment for low BMD, this finding was not statistically significant. Further study is necessary to determine whether HIV infection affects fracture rates after adjustment for low BMD.

In conclusion, among aging HIV-infected men, low BMD was common and HIV infection was significantly associated with modestly lower BMD after adjusting for body weight. Non-black HIV-infected men with lower BMI may be at particular risk for osteopenia or osteoporosis. Among older men with or at risk for HIV infection, decreased BMD is associated with increased fracture risk.

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Table 1

Characteristics of 559 men studied.

Characteristic	HIV-infected (*n* = 328)	HIV-uninfected (*n* = 231)
Age** (mean years ± SD)	54.7 ± 5	55.8 ± 5
Race/ethnicity *n* (%)		
Black	200 (61)	115 (50)
White	39 (12)	45 (19)
Hispanic	77 (23)	64 (28)
Unemployed* *n* (%)	294 (90)	180 (78)
Hypertension*** *n* (%)	135 (41)	122 (53)
Diabetes *n* (%)	47 (14)	36 (16)
Weight* (mean kg ± SD)	77.7 ± 14	83.3 ± 15
Body mass index* *n* (%)		
< 25 kg/m^2 (lean/normal)	159 (48)	70 (30)
25−29.9 kg/m^2 (overweight)	121 (37)	102 (44)
≥ 30 kg/m^2 (obese)	48 (15)	59 (26)
Moderate or strenuous exercise at least once/week *n* (%)	159 (49)	114 (49)
Ever used prednisone *n* (%)	17 (5)	5 (2)
Low testosterone (< 300 ng/dl)	167 (51)	135 (58)
Smoking*** *n* (%)		
Never	32 (10)	23 (10)
Former	95 (29)	42 (18)
Current	201 (61)	166 (75)
Ever used drugs *n* (%)	282 (86)	216 (94)
Recent (past 5 years) heroin use* *n* (%)	80 (24)	87 (38)
Recent (past 5 years) cocaine or crack use*** *n* (%)	163 (50)	135 (58)
Current methadone treatment* *n* (%)	124 (38)	137 (59)
Bone mineral density, femoral neck (g/cm^2)*** (mean ± SD)	0.97 ± 0.14	1.00 ± 0.15
Bone mineral density, lumbar spine (g/cm^2) (mean ± SD)	1.17 ± 0.20	1.20 ± 0.21
T-score, femoral neck*** (mean ± SD)	−0.73 ± 1.09	−0.53 ± 1.18
T-score, lumbar spine (mean ± SD)	−0.60 ± 1.63	−0.32 ± 1.73
Length of HIV diagnosis *n* (%)		
< 5 years	46 (14)	
5−10 years	106 (33)	
> 10 years	172 (53)	
Median CD4 cell count (cells/μl) (range)	390 (3−2424)	
Ever protease inhibitor (PI) use *n* (%)	244 (74)	
Median length of PI use (months) (range)	24 (1−120)	
Ever nucleoside reverse transcriptase inhibitor (NRTI) *n* (%)	294 (87)	
Median length of NRTI use (months) (range)	36 (1−216)	

* $P \leq 0.001$

** $P \leq 0.01$

*** $P \leq 0.05$.

Table 2

Multivariate linear regression analysis of factors independently associated with bone mineral density of the hip or spine.

Characteristic	Femoral neck (β-coefficient)[a]	*P*-value	Lumbar spine (β-coefficient)[a]	*P*-value
Age (per year)	−0.004	0.002	—	—
Non-black race	−0.072	< 0.0001	−0.073	< 0.0001
Weight (per kg)[b]	0.003	< 0.0001	0.003	< 0.0001
HIV-infection	−0.012	0.05	−0.04	0.02
Low testosterone	−0.03	0.01	−0.05	0.002
Ever use of prednisone	—	—	−0.04	0.09
Recent (past 5 years) heroin use	—	—	−1.12	0.26
Current methadone maintenance treatment	—	—	−2.53	0.012

[a] β-coefficients less than zero indicate an inverse association between the characteristic and bone mineral density. Because variables were selected for inclusion in each model only if the univariate association was < 0.2, some variables are excluded from each model.

[b] Substitution of body mass index (kg/m^2) for weight (kg) did not significantly alter the results of either model, nor alter the β-coefficients or *P*-values of the other variables in either model.

Table 3

Multivariate linear regression analysis of factors independently associated with bone mineral density of the hip or spine among HIV-infected men.

Characteristic	Femoral neck (β-coefficient)[a]	*P*-value	Lumbar spine (β-coefficient)[a]	*P*-value
Age (per year)	−0.0001	NS	0.006	0.03
Non-black race	−0.018	0.004	−0.06	0.02
Weight (per kg)[b]	0.003	< 0.0001	0.003	0.002
Low testosterone	−0.02	NS	−0.075	0.002
HIV infection > 10 years	−0.004	NS	−0.075	0.003
Duration of antiretroviral use (months)	−0.0004	NS	0.0001	NS
Duration of protease inhibitor use (months)	0.0006	NS	0.0003	NS
CD4 cell count < 200 cells/μl	0.003	NS	−0.03	NS

[a] β-coefficients less than zero indicate an inverse association between the characteristic and bone mineral density.

[b] Substitution of body mass index (kg/m^2) for weight (kg) did not significantly alter the results of either model, nor alter the β-coefficients or *P*-values of the other variables in either model.

Table 4

Factors independently associated with incident fractures in multivariate analysis.

Characteristic	Hazard ratio (95% confidence interval)	*P*-value
Age	0.96 (0.89−1.05)	NS
Body mass index	1.03 (0.95−1.10)	NS
Race		
White (referent)	1.0	
Hispanic	0.96 (0.40−2.34)	NS
Black	0.37 (0.14−0.98)	0.04
HIV infection	1.38 (0.63−3.01)	NS
Low BMD (osteopenia or osteoporosis)	2.90 (1.16−7.27)	0.02

BMD, bone mineral density.