MAJOR ARTICLE

Low Bone Mineral Density, Regardless of HIV Status, in Men Who Have Sex With Men

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A high prevalence of low bone mineral density (BMD) has been reported among men with primary or chronic human immunodeficiency virus (HIV) infection. To gain further insight into the contribution of HIV infection, we compared the BMD of 41 men who have sex with men (MSM) with primary HIV infection, 106 MSM with chronic HIV infection, and a control group of 30 MSM without HIV infection. Low BMD, defined as a *z* score of ≥2.0 SDs below the mean at the lumbar spine or hip, was highly prevalent in all 3 groups. In the multivariate analyses, HIV infection was not associated with BMD, suggesting that low BMD previously reported in HIV-infected MSM may predate HIV acquisition.

Keywords. Bone mineral density; chronic HIV infection; HIV-negative controls; men who have sex with men; primary HIV infection.

Multiple studies have shown that human immunodeficiency virus (HIV)–infected persons have a higher prevalence of low bone mineral density (BMD), compared with the general population [1]. In addition to traditional risk factors for low BMD, HIV infection alone and HIV infection plus exposure to combination antiretroviral therapy (cART) have been suggested as contributing factors [1].

Recently, we reported a high prevalence of low BMD in the absence of markers of increased bone turnover in a cohort of men with primary HIV infection. Low BMD was associated with older age, lower body mass index (BMI; defined as the weight in kilograms divided by the height in meters squared), decreased thyroid-stimulating hormone levels, and higher HIV viremia [2]. Because these patients were cART naive, our findings raised the question of whether low BMD was related to recent acquisition of HIV, whether it was related to other conventional risk factors affecting BMD that might be more prevalent among HIV-infected persons, or whether it predated HIV acquisition. To gain further insight into the contribution of HIV infection, we compared BMD and biochemical markers of bone metabolism among men who have sex with men (MSM) who had untreated primary or chronic HIV infection with those in a control group of MSM without HIV infection.

METHODS

Between January 2008 and 2011, dual-energy X-ray absorptiometry (DEXA) was prospectively performed for all cART-naive HIV-positive patients presenting for care at the Academic Medical Center in Amsterdam, the Netherlands. In the present study, we included all MSM with primary HIV infection (n = 41) or chronic HIV infection (n = 106) aged 20–55 years for whom DEXA was performed during this period.

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Primary HIV infection was defined as a negative or indeterminate Western blot finding in combination with detectable plasma HIV-1-RNA, or, in case of a positive Western blot result, a negative HIV screening result within the previous 180 days [3]. Thirty MSM with primary HIV infection were described in our previous article [2], and 11 additional MSM with primary HIV infection who presented between November 2009 and December 2010 were added to this cohort. The MSM with chronic HIV infection were cART-naive patients who were not classified as having primary HIV infection. Controls were 30 HIV-seronegative MSM who participate in the Amsterdam Cohort Studies and are at risk for HIV infection [4], had a follow-up visit at the Municipal Public Health Service of Amsterdam between March and July 2010, and were aged 20–55 years . We assumed that these HIV-negative controls had lifestyles that were comparable to those of the HIV-infected MSM.

Exclusion criteria in all 3 cohorts were medical conditions known to affect bone metabolism (eg, chronic renal disease and hypercalcemia), injection drug use, and corticosteroid therapy use for ≥3 months. The study was approved by the Ethics Committee of our hospital. All participants provided written informed consent.

Sociodemographic characteristics were obtained from all participants through a questionnaire. For the MSM with primary HIV infection and the HIV-negative controls, we additionally assessed risk factors for low BMD (eg, smoking, alcohol or drug use, dairy food intake, and history of bone fracture) through a questionnaire and collected blood for evaluation of biochemical markers relevant to bone metabolism, including bone-formation markers (alkaline phosphatase and procollagen type 1 N-terminal propeptide [P1NP]) and bone-resorption markers (C-terminal telopeptide of type 1 collagen [1CTP] and C-telopeptide crosslink of type 1 collagen [CTX]) at enrollment. Calcium, phosphate, alkaline phosphatase, thyroid-stimulating hormone, and 25-hydroxyvitamin D were analyzed by an immunoturbidimetric method (Roche Diagnostics, Manheim, Germany). Testosterone was analyzed by an in-house radioimmunoassay, and sex-hormone-binding globulin (SHBG) was analyzed by an immunoradiometric assay (Orion Diagnostica, Espoo, Finland). P1NP and 1CTP were analyzed by a radioimmunoassay (Orion Diagnostica), and CTX was determined by an immunometric assay (Roche Diagnostics, Indianapolis, IN).

BMDs of the lumbar spine (L1–L4), femoral neck, and total hip regions were measured by DEXA, using the Hologic QDR 4500W densitometer, with software version 12.4. The reference database of the National Health and Nutrition Examination Survey (NHANES) IV was used for calculating lumbar spine and hip *T* and *z* scores. *T* scores refer to the number of SDs below the mean BMD for young, healthy adults matched for sex and ethnicity, and *z* scores refer to the number of SDs below the mean BMD for an age, sex, and ethnicity-matched reference population. The International Society for Clinical Densitometry defines low BMD in men aged <50 years as a *z* score of ≥2.0 SDs below the mean at either the spine or hip and states that in this age group osteoporosis should not be diagnosed on the basis of BMD measurements alone [5]. We therefore did not further distinguish between osteopenia or osteoporosis.

Mean *T* and *z* scores of the lumbar spine, femoral neck, and total hip regions of MSM with primary or chronic HIV infection and HIV-negative controls were compared to those of the reference population by 1-sample *t* tests. Patient characteristics and BMD were compared between the 3 groups, using 1-way analysis of variance or independent-sample *t* tests, for continuous data, and χ^2 or Fisher exact tests, for categorical data. Given a common SD of about 0.9 for BMD *z* scores in the 3 groups and sample sizes of 41 MSM with primary HIV infection, 106 with chronic HIV infection, and 30 HIV-negative controls, we had 80% power to detect a difference of ±0.68 in BMD *z* scores when comparing MSM with primary HIV infection to HIV-negative controls, a difference of ±0.58 when comparing MSM with chronic HIV infection to HIV-negative controls, and a difference of ±0.52 when comparing MSM with primary HIV infection to those with chronic HIV infection. The association of HIV with *T* and *z* scores was examined using multivariable linear regression, with adjustment for BMI and, in the case of *T* scores, also for age. Multivariable models were constructed separately for all 3 measured bone sites. Analyses were conducted using SPSS, version 18.0. *P* values of < .05 were considered statistically significant.

RESULTS

Forty-one MSM with primary HIV infection, 106 cART-naive MSM with chronic HIV infection, and 30 unmatched HIV-negative controls were included in this study. Patient characteristics, bone metabolism markers, and BMD are summarized in Table 1. Thirty MSM with primary HIV infection (73%) had negative or indeterminate Western blot findings (Fiebig stage I-IV), 33 (81%) had symptomatic primary HIV infection, and all but 1 were cART naive (this patient had 9 days of cART exposure). The median interval between diagnosis and DEXA was 28 days (interquartile range, 20–43 days). For MSM with chronic HIV infection, the duration of infection was not known. DEXA was performed at their initial visit to our hospital, prior to starting cART. Among MSM with primary and chronic HIV infection, the mean plasma HIV-1-RNA loads (±SD) were 5.3 ± 1.2 and 4.5 ± 0.9 $\log_{10}$ copies/mL, respectively, and the mean $CD4^+$ T-cell counts (±SD) were 543 ± 253 and 438 ± 214 cells/mm^3, respectively. All participants denied prior injection drug or corticosteroid use.

Table 1. Characteristics of Men Who Have Sex With Men (MSM), by Human Immunodeficiency Virus (HIV) Status

Characteristic	HIV Negative (n = 30)	Primary HIV Infection (n = 41)	Chronic HIV Infection (n = 106)	P[a]
Demographic				
Age, y	38 (6)	38 (9)	36 (8)	.6
Weight, kg	82.0 (21.1)	73.6 (11.5)	73.7 (11.3)	.009
BMI[b]	24.4 (4.8)	22.7 (3.1)	22.7 (2.9)	.04
White race	24 (80)	34 (83)	85 (80)	.9
Risk factors for low BMD				
Current smoking	7 (23)	18 (44)	NA	.07
Alcohol use of ≥3 units/d	7 (23)	7 (17)	NA	.5
Current recreational drug use	15 (50)	27 (66)	NA	.2
Dairy food intake of ≥3 products/week	28 (93)	35 (90)[c]	NA	.7
Multivitamin use	15 (50)	22 (56)[c]	NA	.6
History of bone fracture	13 (43)	15 (39)[c]	NA	.7
Strenuous physical activity of 20 min ≥3 times/wk	16 (53)	25 (64)[c]	NA	.4
Biochemical markers relevant for bone metabolism[d]				
Calcium level,[e] mmol/L (2.2–2.6 mmol/L)	2.22 (0.14)	2.17 (0.08)	NA	.08
Phosphate level, mmol/L (0.7–1.45 mmol/L)	1.32 (0.23)	0.93 (0.18)	NA	<.001
Alk phos level, U/L (40–120 U/L)	59 (18)	69 (21)	NA	.04
25-hydroxyvitamin D level, nmol/L (28–107 nmol/L)	64 (27)	75 (37)[c]	NA	.2
TSH level, mE/L (0.5–5 mE/L)	1.8 (0.8)	1.6 (0.8)[g]	NA	.2
Testosterone level, nmol/L (11–35 nmol/L)	19 (6)	21 (6)[f]	NA	.1
SHBG level, nmol/L (12–75 nmol/L)	31 (11)	40 (16)[f]	NA	.01
FAI[h] (20–90)	65 (18)	63 (38)[f]	NA	.8
P1NP level, μg/L (22–87 μg/L)	52 (13)	42 (16)[c]	NA	.009
1CTP level, μg/L (2.1–5.0 μg/L)	3.2 (0.7)	3.3 (1.1)[c]	NA	.7
CTX level, ng/L (<584 ng/L)	154 (93)	288 (196)[c]	NA	.001
Bone mineral density				
Lumbar spine (L1–L4)				
BMD, g/cm^2	1.0 (0.13)	0.96 (0.12)	0.93 (0.33)	.4
T score	−0.9 (1.1)	−1.2 (1.1)	−1.1 (1.1)	.4
z score	−0.8 (1.1)	−1.1 (1.1)	−1.0 (1.1)	.4
Femoral neck				
BMD, g/cm^2	0.84 (0.1)	0.84 (0.12)	0.85 (0.13)	.8
T score	−0.7 (0.7)	−0.7 (0.9)	−0.7 (0.9)	1.0
z score	−0.3 (0.7)	−0.3 (0.8)	−0.3 (0.9)	1.0
Total hip				
BMD, g/cm^2	0.99 (0.11)	0.97 (0.12)	0.98 (0.14)	.8
T score	−0.3 (0.7)	−0.4 (0.8)	−0.4 (0.8)	.8
z score	−0.1 (0.7)	−0.3 (0.8)	−0.3 (0.8)	.7

Data are no. (%) of patients or mean (SD).

Abbreviations: Alk phos, alkaline phosphatase; CTX, C-telopeptide cross-link of type 1 collagen; NA, not available; P1NP, procollagen type 1 N-terminal propeptide; SHBG, sex hormone–binding globulin; TSH, thyroid-stimulating hormone; 1CTP, C-terminal telopeptide of type 1 collagen.

[a] Based on 1-way analysis of variance or independent *t* tests, for continuous variables, and χ^2 or Fisher exact tests, for proportions.

[b] Body mass index (BMI) is calculated as the weight in kilograms divided by the height in meters squared.

[c] Two patients had missing results.

[d] Reference values are specified in parentheses.

[e] Corrected for albumin level.

[f] One patient had missing results.

[g] Four patients had missing results.

[h] Free androgen index (FAI) is calculated as [(testosterone level) × (100/SHBG level)].

HIV-infected MSM had a significantly lower mean body weight ($P = .009$) and a lower BMI ($P = .04$) than HIV-negative MSM. Additional risk factors and bone metabolism markers were assessed in MSM with primary HIV infection and HIV-negative controls. Except for a higher percentage of smokers among MSM with primary HIV infection, risk factors for low BMD were not significantly different between these men and HIV-negative controls. Five MSM with primary HIV infection (13%) and 3 HIV-negative controls (10%) had low 25-hydroxyvitamin D levels ($P = 1.0$), and 0 and 2 (7%), respectively, had low testosterone levels ($P = .2$). Levels of serum phosphate and the bone-formation marker P1NP were lower, and levels of alkaline phosphatase, SHBG, and the bone-resorption marker CTX were significantly higher among MSM with primary HIV infection, yet all values were within reference ranges (Table 1).

Mean *T* and *z* scores for MSM with primary or chronic HIV infection and HIV-negative controls were compared to those for the reference population. With the exception of the total hip *z* score for HIV-negative controls, the lumbar spine, femoral neck, and total hip *T* and *z* scores for all 3 groups yielded SDs that were statistically significantly below the mean of the reference population, indicating that the average bone densities in our study populations were lower than the average bone density of the NHANES IV reference population. Lumbar spine BMD and *T* and *z* scores were slightly but not significantly lower among the HIV-infected MSM, compared with the HIV-negative controls. Femoral neck and total hip BMD and *T* and *Z* scores were not different for MSM with primary and chronic HIV infection. BMD did not differ significantly between MSM with primary and those with chronic HIV infection.

Eight MSM (20%) with primary HIV infection, 23 MSM (22%) with chronic HIV infection, and 4 HIV-negative controls (13%) had low BMD at ≥1 of the 3 bone sites ($P = .6$).

In the multivariable analyses, primary and chronic HIV infection, compared with HIV negativity, were not associated with lumbar spine, femoral neck, and total hip *z* scores. BMI was positively associated with *z* scores for all 3 bone sites (Table 2). The association of the various parameters with *T* scores was comparable (data not shown).

Table 2. Multivariable Linear Regression Analysis of Variables Associated With Lumbar Spine, Femoral Neck, and Total Hip *z* Scores Among Human Immunodeficiency Virus (HIV)–Infected Men Who Have Sex With Men

Region, Variable	β[a] (95% CI)	*P*
Lumbar spine		
Primary HIV infection[b]	−0.2 (−.7 to .3)	.4
Chronic HIV infection[b]	−0.1 (−.6 to .4)	.7
BMI[c]	0.08 (.03 to .1)	.001
Femoral neck		
Primary HIV infection[b]	0.2 (−.2 to .5)	.4
Chronic HIV infection[b]	0.2 (−.2 to .5)	.3
BMI[c]	0.1 (.06–.1)	<.001
Total hip		
Primary HIV infection[b]	0.04 (−.3 to .4)	.8
Chronic HIV infection[b]	0.03 (−.3 to .3)	.8
BMI[c]	0.09 (.06 to .1)	<.001

Abbreviation: CI, confidence interval.

[a] Values of <0 indicate an inverse association between *z* score and the parameter.

[b] The reference group is the HIV-negative control group.

[c] Body mass index (BMI) is calculated as the weight in kilograms divided by the height in meters squared.

DISCUSSION

We found significantly decreased mean *T* and *z* scores and a high prevalence of low BMD among MSM with untreated primary or chronic HIV infection, as well as among HIV-negative MSM. Lumbar spine *T* and *z* scores for MSM with primary or chronic HIV infection were slightly but nonsignificantly lower than those for HIV-negative controls, which could be explained by the significantly lower BMI of these patients. In the multivariable analysis, HIV infection was not associated with BMD, suggesting that at least part of the loss in BMD previously reported in HIV-infected MSM predates HIV acquisition.

Our findings are in agreement with recently presented preliminary data, which showed comparable BMDs between 43 untreated adults with chronic HIV infection and 35 age-, sex-, and race-matched HIV-negative controls [6]. Moreover, 2 antiretroviral preexposure prophylaxis trials reported a 10%–14% prevalence of low BMD (defined as a *z* score of ≥2.0 SDs below the mean) in healthy, HIV-seronegative MSM who were at risk for HIV infection [7, 8]. One of these studies observed that low BMD was associated with inhalant (ie, poppers and amyl nitrates) use and amphetamine use [7].

Numerous studies reported a high prevalence of low BMD among subjects with chronic HIV infection, which, in addition to traditional risk factors, is usually attributed to HIV infection alone and to HIV infection plus the use of cART. A meta-analysis revealed a 6.4-fold higher odds of low BMD (defined as a *T* score of >1.0 SD below the mean) among HIV-infected individuals, compared with HIV-negative controls [9]. However, most of the studies included in this meta-analysis used as healthy controls individuals from the general population, who might have lifestyle risk factors related to low BMD that substantially differ from those of the HIV-infected population. Indeed, (traditional) risk factors for low BMD, such as low body weight, smoking, alcohol use, and recreational drug use, are likely to be more prevalent among MSM than among heterosexual men [10–12]. Therefore, to precisely

measure the effect of HIV infection on BMD among MSM, it is important to use adequate control groups composed of HIV-negative MSM.

One might argue that the moment of BMD measurement among MSM with primary HIV infection was too early during infection for significant HIV-associated changes to have occurred. However, comparison of the mean *T* and *z* scores of MSM with primary HIV infection with those of MSM with chronic HIV infection revealed similar, equally low BMDs, suggesting that more-prolonged untreated HIV infection by itself did not contribute significantly to the observed low BMD.

Low levels of bone-formation markers and high levels of bone-resorption markers were detected in MSM with primary HIV infection, compared with HIV-negative controls, suggesting an increase in bone turnover as a result of primary HIV infection. This may be explained by the acute inflammation associated with primary HIV infection, which might induce bone loss by promoting bone destruction by osteoclasts and by inhibiting bone formation by osteoblasts [13]. In patients with acute hepatitis A and B, bone formation was found to be transiently decreased, reflecting a state of low bone turnover during the acute illness [14]. However, the biochemical evidence for increased bone turnover in MSM with primary HIV infection may be transient and possibly may not result in significant bone loss, given the very similar BMD for MSM with chronic HIV infection. Nevertheless, prolonged HIV infection and use of cART may still have an additional negative impact on BMD. Interestingly, serum phosphate levels were significantly lower in MSM with primary HIV infection, which may reflect renal tubular dysfunction as a result of HIV infection of the renal tubular epithelium, as has been reported previously in a patient with primary HIV infection [15].

Our study has several limitations. Risk factors for low BMD and bone-metabolism markers were not recorded prospectively for MSM with chronic HIV infection. Second, the sample sizes of the primary HIV infection and HIV-negative cohorts were too small to detect significant associations between low BMD and conventional risk factors, other than age and BMI, affecting bone health. Third, 80% of participants were white. Finally, because of the cross-sectional design, we cannot infer causal relationships.

In conclusion, we found significantly decreased *T* and *z* scores and a similarly high prevalence of low BMD among MSM with untreated primary or chronic HIV infection, as well as among HIV-negative MSM. This suggests that the low BMD found in MSM with untreated acute or chronic HIV infection may predate HIV acquisition and that low BMD is not fully attributable to HIV infection alone or to HIV infection plus the use of cART. Our results also emphasize the need for adequate control groups with similar risk exposures in future studies that assess BMD and its changes over time in persons living with HIV.

Notes

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M. L. G., P. R., and J. M. P. drafted the manuscript. M. L. G. and F. W. N. M. W. conducted the statistical analysis. M. L. G. and J. M. P. established the Primo-S. H. M. cohort, S. M. E. V. and J. M. P. established the chronically HIV-infected cohort, and I. G. S. and M. P. established the HIV-negative cohort. All authors provided valuable input into protocol development and interpretation of data and critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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