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ORIGINAL ARTICLE

Association between HIV infection and bone mineral density in climacteric women

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Abstract
Summary A cross-sectional study was conducted with the purpose of evaluating bone mineral density in HIV seropositive and seronegative climacteric women. HIV infection was negatively associated with bone mineral density in the lumbar spine
Purpose To assess bone mineral density (BMD) and its associated factors in HIV seropositive and seronegative climacteric women
Methods A cross-sectional study with 537 women (273 HIV seropositive and 264 HIV seronegative) aged between 40 and 60 years old receiving follow-up care at two hospitals in Brazil. A questionnaire on clinical and sociodemographic characteristics was completed. Laboratory tests were performed, and BMD was measured at the lumbar spine and hip. Statistical analysis was carried out by Yates and Pearson chi-squared tests, Mann–Whitney test, and multiple linear regression.
Results The mean age was 47.7 years in HIV-seropositive women, and 75 % had nadir CD4 above 200, and 77.8 % had viral load below the detection limit. The mean age in the HIV-seronegative women was 49.8 years. The prevalence of low spinal BMD was 14.6 % in the HIV-seropositive and 4.6 % in the HIV-seronegative women ($p<0.01$). The prevalence of low BMD at the femoral neck was 5.6 % in HIV-seropositive and 3.3 % in the HIV-seronegative women ($p=0.38$). Multiple analyses showed that the factors associated with lower BMD at the spine were being postmenopausal and being HIV-seropositive. Being overweight was associated with a higher BMD. At the femoral neck, factors associated with lower BMD were being postmenopausal and being white. Being overweight and having a greater number of pregnancies were associated with higher BMD
Conclusions HIV-seropositive women on long-term antiretroviral treatment and in good immunological conditions exhibited low BMD in the spine (L1–L4). However, BMD in the femoral neck was similar to non-infected women.

Keywords Metabolic bone diseases · Osteoporosis · HIV · HIV seropositivity · Menopause · Climacteric

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Introduction

The widespread use of antiretroviral therapy has reduced mortality in HIV-seropositive individuals [1]. As access to antiretroviral therapy has increased around the world, including Brazil, the number of HIV-seropositive people over 50, especially women, has increased [2]. HIV-seropositive individuals have shown a decline in infections and malignancies associated with HIV, but there has been an increase in morbidities due to aging. The incidence of diseases such as osteoporosis is higher in HIV-seropositive patients than in HIV-seronegative patients of the same sex and age, after accounting for other risk factors [3, 4]. Furthermore, HIV infection may accelerate aging and promote earlier occurrence of such comorbidities [5, 6].

Osteoporosis is a common degenerative disease that has a significant impact on morbidity and mortality in older age

groups, particularly among women [7]. Low bone mass occurs in an estimated quarter of the world population, including 30 % of postmenopausal women [8]. Low bone mass compromises bone strength and increases the risk of fractures, which has a negative impact on quality of life, morbidity, and mortality [9]. In a meta-analysis of 20 studies that included 884 HIV-seropositive patients and 654 seronegative controls, Brown and Qaqish reported a prevalence of 67 % of low bone mass and 15 % of osteoporosis in the HIV-seropositive group, resulting in relative risks of 6.4 for low bone mass and 3.7 for osteoporosis compared with HIV-seronegative controls [3]. However, in a prospective study of 241 HIV-seropositive and 219 HIV-seronegative women, HIV status was not associated with low bone mass [10].

A recent meta-analysis suggests that HIV infection is associated with a modest increase in the incidence of fractures [11], although not all studies have shown an increase [12]. The physiological mechanism(s) that lead to loss of bone mineral mass in this population is complex and can include factors related to HIV infection as well as antiretroviral therapy [10]. Furthermore, long periods of amenorrhea that occur in these women may explain the estrogen depletion that often occurs. This depletion can affect bone health, because estrogen is a protective factor [13–15]. There are also other factors associated with bone loss, such as smoking, alcohol consumption, and low weight, which seem to be more frequent in HIV-infected women [10].

Climacteric women is one group in which HIV infection is becoming more common in Brazil, as in the rest of the world [13]; in these women, one of the expected consequences is bone damage. However, few studies have evaluated the association between HIV infection and bone mineral density (BMD) in climacteric women. We have assessed whether HIV infection is associated with low BMD and have evaluated other factors that may interfere with bone mineral density in these climacteric women.

Methods

We conducted a cross-sectional study between October 2010 and July 2012. The sample size calculation was based on a mean difference in BMD at the lumbar spine of 0.05 g/cm^2 between HIV-seronegative and HIV-seropositive women [16]. The sample size per group was calculated at 241 women, including a 15 % increase for possible losses (α=0.05, β=0.20).

Women aged between 40 and 60 years old who were receiving follow-up care in the Menopause, Genital Infections and Infectious Diseases Outpatient Units of the State University of Campinas (Unicamp) and at the Infectious Diseases Outpatient Unit at Eduardo de Menezes Hospital in Belo Horizonte were invited to participate in the study. A total of 559 women were invited, with a refusal rate of 4 %. The main reasons for refusal were lack of time and difficulty returning to the hospital to complete the required exams. Thus, interviews were conducted with 537 women (273 HIV-seropositive and 264 HIV-seronegative). Of these 537 women, 34 HIV-seropositive and 16 HIV-seronegative failed to answer the questionnaire correctly or did not return to the hospital for the required exams.

For inclusion in the HIV-seropositive group, patients had ELISA and Western blot laboratory confirmation tests, while women recruited to the HIV-seronegative group tested negative for HIV. Exclusion criteria were lactating women, women with bilateral oophorectomy, those who used progestogens or medications that could interfere with bone metabolism, and those unable to answer the questionnaire.

All women were interviewed in a private environment, and a questionnaire on sociodemographic, behavioral, and clinical characteristics was completed. Weight and height were measured, laboratory tests were performed (follicle-stimulating hormone [FSH], luteinizing hormone [LH], estradiol, thyroid-stimulating hormone [TSH], free thyroxine [FT4], fasting glucose, total cholesterol and its fractions), and measurements of BMD were taken.

Bone mineral density was measured at the lumbar spine, femoral neck, and total hip by dual energy X-ray absorptiometry (DXA), on a GE-Lunar Radiation Corporation device (Madison, Wisconsin, USA) and expressed in g/cm^2. Women in premenopause (regular menses) or perimenopause (irregular menses) were classified according to current international criteria, using a *Z*-score that compares BMD with references of the same age, sex, and ethnicity in a healthy population. In these women, low BMD or osteoporosis was defined as a *Z*-score below −2.0 SD at the lumbar spine, femoral neck, or total hip. For postmenopausal women (no menses for 1 year), *T*-score was used and low BMD or osteoporosis was defined as a *T*-score below −2.5 SD at the lumbar spine, femoral neck, or total hip [17–19]. The independent variables were HIV group (positive/negative), age (years), skin color (white or non-white), physical activity in the last month (none or up to two times per week/≥3 times per week), smoking (yes/no or in the past), alcohol consumption (yes/no or never drank), amount of alcohol consumption (more than one dose per day/one dose or less per day or unknown), number of pregnancies (up to 2/≥3), menopausal status (premenopause/perimenopause/postmenopause), use of hormone replacement therapy in the last month (yes/no), history of fractures (yes/no), history of spine, hip, and/or forearm fracture after the age of 40 (yes/no), use of antiretroviral therapy (yes/no), hypothyroidism (yes/no), BMI (<25/≥25.0 kg/m^2), FSH (<40/≥40 mIU/ml); TSH (normal/hypothyroidism or hyperthyroidism), and free T4 (normal/abnormal).

Two-dimensional contingency tables were prepared for each dependent variable according to the various independent

Table 1 Characteristics of menopausal women in HIV seropositive and seronegative groups (n=537)

Characteristics	Group		p Value
	HIV seropositve (n=273)	HIV seronegative (n=264)	
Age (years)			
40–44	36.6 %	20.4 %	<0.01#
45–49	27.5 %	28.0 %	
50–54	19.0 %	27.7 %	
≥55	16.9 %	23.9 %	
BMI (kg/m^2)			
<20.00	12.5 %	1.5 %	<0.01#
20.00–24.99	39.1 %	27.8 %	
25.00–29.99	35.4 %	36.9 %	
≥30.00	12.9 %	33.8 %	
Skin color			
White	40.2 %	48.2 %	0.07#
Black	11 %	12.9 %	
Mulatto	46.4 %	36.9 %	
Asian	1.8 %	1.9 %	
Indígenous	0.4 %	0 %	
Number of pregnancies			
0	6.6 %	8.4 %	0.52#
≥1	93.4 %	91.6 %	
Schooling (years)			
≤7	58.2 %	39.4 %	<0.01#
8–11	26.7 %	37.9 %	
≥12	15.1 %	22.7 %	
Menopausal status			
Premenopause	33.7 %	22.0 %	<0.01#
Perimenopause	25.6 %	20.0 %	
Postmenopause	40.7 %	58.0 %	
Smoking			
Yes	28.6 %	14.8 %	<0.01#
No	50.9 %	58.0 %	
Unknown	20.5 %	27.2 %	
Amount of alcohol consumption (More than one dose a day)			
Yes	29.7 %	12.6 %	<0.01#
No	36.3 %	78.6 %	
Unknown	34.0 %	8.8 %	
Bone mass (L1–L4)			
Normal	85.45 %	95.4 %	<0.01#
Low	14.5 %	4.6 %	
Bone mass (femoral neck)			
Normal	94.4 %	96.74 %	0.38#
Low	5%	3.3 %	
BMD (g/cm^2) (L1–L4)			
HIV+	1.08	(0.62–1.55)	0.43*
HIV−	1.10	(0.75–1.80)	
BMD (g/cm^2) (femoral neck)			
HIV+	0.90	(0.54–1.90)	0.05*
HIV−	0.91	(0.30–1.67)	
Z-score (L1–L4)			
HIV+	−0.70	(−2.70–2.59)	0.43*

Table 1 (continued)

Characteristics	Group		*p* Value
	HIV seropositve (n=273)	HIV seronegative (n=264)	
HIV−	0.68	(−1.89–4.0)	
Z-score (femoral neck)			
HIV+	−0.16	(−2.12–5.69)	0.52*
HIV−	0.13	(−3.47–4.35)	

#Pearson's chi-squared; Yates's chi-squared

*Mann–Whitney test

variables in both groups. Yates and Pearson chi-squared tests and Mann–Whitney test were used to compare the associated factors [20]. Multiple linear regression analysis [21] was performed to assess the factors associated with BMD (g/cm^2) in the lumbar spine and femoral neck. For this, in the statistical model, all variables associated with BMD were considered. In addition, variables having "p value" greater than 0.05 were eliminated from the model. The computer programs used to process and analyze data was SPSS (version 17.0) and Stata (version 7.0).

Results

The mean age was 47.7 years in HIV-seropositive women and 49.8 years in HIV-seronegative women (p<0.001). In the HIV-seropositive group, the mean duration of HIV infection was 9.9 (±5.4) years and 92 % were on antiretroviral therapy (ART), with a mean time of ART of 9.4 (±4.8) years. In the HIV-seropositive group, 75 % of the women had CD4 nadir ≥200 cells/mm^3, and 61.8 % of the women had the last cell count >500 cells/mm^3, whereas only 7.5 % had the last cell

Table 2 BMD (g/cm^2) in the spine (L1–L4) and variables of health care

	Study group		
	HIV seropositive (n=239) Mean [SD] (n)	HIV seronegative (n=248) Mean [SD] (n)	*p Value
Age (years)			
40–49	1.13 [0.16] (149)	1.13 [0.18] (114)	0.50
50–60	1.00 [0.17] (90)	1.08 [0.18] (134)	<0.01
Skin color			
Non-white	1.09 [0.17] (138)	1.10 [0.17] (127)	0.68
White	1.06 [0.18] (101)	1.11 [0.18] (121)	0.13
No. of pregnancies			
≤2	1.09 [0.17] (96)	1.13 [0.18] (134)	0.27
≥3	1.07 [0.18] (143)	1.07 [0.17] (113)	0.71
Smoking			
No	1.08 [0.18] (167)	1.11 [0.18] (212)	0.34
Yes	1.07 [0.16] (72)	1.07 [0.17] (36)	0.64
More than one drink a day			
No	1.07 [0.18] (170)	1.10 [0.18] (217)	0.16
Yes	1.11 [0.16] (69)	1.11 [0.17] (30)	0.86
FSH (mUI/ml)			
<40	1.14 [0.15] (130)	1.17 [0.18] (93)	0.04
≥40	1.00 [0.17] (104)	1.07 [0.16] (146)	<0.01
Menopausal status			
Premenopause/perimenopause	1.14 [0.15] (139)	1.18 [0.19] (100)	0.10
Postmenopause	0.99 [0.18] (100)	1.05 [0.15] (148)	0.01
BMI (kg/m^2)			
<25	1.05 [0.17] (122)	1.06 [0.16] (74)	0.74
≥25	1.10 [0.18] (115)	1.17 [0.18] (173)	0.87

*Mann–Whitney test

count <200 cells/mm^3. Viral load was undetectable in 77.8 % of the HIV-seropositive women with available data. The predominant mode of HIV acquisition in this cohort was heterosexual acquisition (71.1 %). The other modes of acquisition were illicit drug use (2.2 %) and blood transfusion (1.1 %). Of the HIV-seropositive women, 19.8 % did not know and 5.8 % did not answer this question. Most HIV-seropositive women had a body mass index <25 kg/m^2 (51.6 %), while in the HIV-seronegative women with a BMI<25 kg/m^2 accounted for 29.3 % (p<0.001). The prevalence of low spinal bone mass or osteoporosis (Z-score<−2 SD or T-score<−2.5 SD) was 14.6 % in the HIV-seropositive group and 4.6 % in the HIV-seronegative group (p<0.01). The mean BMD at the spine was 1.08 (0.62 to 1.55) g/cm^2 in the HIV-seropositive group and 1.10 (0.75 to 1.80) g/cm^2 in the HIV-seronegative group (p=0.43). The prevalence of low bone mass or osteoporosis at the femoral neck was 5.6 % in HIV-seropositive group and 3.3 % in the HIV-seronegative group (p=0.38). The mean BMD at the femoral neck was 0.90 (0.54 to 1.90) g/cm^2 in the HIV-seropositive group and 0.91 (0.30 to 1.67) g/cm^2 in the HIV-seronegative group (p=0.053) (Table 1).

In bivariate analysis, factors associated with lower BMD at the spine were older age (p<0.001), FSH>40 mIU/ml (p=0.007) and being postmenopausal (p=0.011) (Table 2). The only factor associated with lower BMD at the femoral neck was older age (p=0.002) (Table 3). Multiple linear regression analysis showed that the factors associated with lower BMD at the spine were being postmenopausal and being HIV-seropositive. Being overweight was associated with a higher BMD. At the femoral neck, factors associated with lower BMD were being postmenopausal and being white, while being overweight and having a greater number of pregnancies were associated with higher BMD (Table 4).

Discussion

The aim of this study was to evaluate bone mineral density and its associated factors in HIV seropositive and seronegative climacteric women. We have observed BMD in the lumbar spine (L1–L4) decreased in 14.6 % in the HIV-seropositive women and 4.6 % in the HIV-seronegative women (p<0.01),

Table 3 BMD (g/cm^2) in the femoral neck and variables of health care

	Study group		
	HIV seropositive (n=211) Mean (SD) n	HIV seronegative (n=248) Mean (SD) n	*p Value
Age (years)			
40–49	0.93 [0.19] (134)	0.92 [0.19] (114)	0.79
50–60	0.84 [0.16] (77)	0.90 [0.17] (134)	<0.01
Color			
Non-white	0.92 [0.17] (115)	0.92 [0.18] (127)	0.80
White	0.88 [0.19] (96)	0.89 [0.16] (121)	0.46
No. of pregnancies			
≤2	0.88 [0.19] (89)	0.90 [0.17] (134)	0.21
≥3	0.92 [0.17] (122)	0.92 [0.17] (113)	0.95
Smoking			
No	0.90 [0.17] (152)	0.92 [0.17] (212)	0.35
Yes	0.91 [0.21] (59)	0.86 [0.15] (36)	0.39
More than one drink a day			
No	0.90 [0.18] (148)	0.91 [0.17] (217)	0.40
Yes	0.91 [0.17] (63)	0.89 [0.17] (30)	0.90
FSH (mUI/ml)			
<40	0.93 [0.17] (116)	0.96 [0.17] (93)	0.15
≥40	0.87 [0.19] (92)	0.88 [0.16] (146)	0.24
Menopausal status			
Premenopause/perimenopause	0.95 [0.19] (122)	0.96 [0.18] (100)	0.34
Postmenopause	0.84 [0.15] (89)	0.88 [0.16] (148)	0.12
BMI (kg/m^2)			
<25	0.85 [0.17] (106)	0.85 [0.13] (74)	0.94
≥25	0.95 [0.19] (103)	0.93 [0.18] (173)	0.57

*Mann–Whitney test

Table 4 Variables associated with BMD (g/cm^2)—multiple linear regression

	EC	SD	*p* Value
L1–L4 (*n*=452)			
Postmenopause	−0.137	0.016	<0.01
BMI (≥25.0)	0.048	0.016	<0.01
HIV seropositive	−0.037	0.016	0.02
Constant	1.154	0.018	<0.01
Femoral neck (*n*=428)			
Postmenopause	−0.085	0.016	<0.01
BMI (≥25.0)	0.082	0.016	<0.01
Skin color (white)	−0.040	0.016	<0.02
No. of pregnancies (≥3)	0.038	0.017	0.02
Constant	0.903	0.019	<0.01

Considered predictors: study group (HIV+ 1/control 0), age (years), skin color (white 1/non-white 0), physical activity in the last month (none or up to two times per week 0/≥3 times per week 1), smoking (yes 1/no or in the past 0), alcohol consumption (yes 1/no or never drank 0), amount of alcohol consumption (more than one dose per day 1/one dose or less per day or unknown 0), number of pregnancies (up to 2 0/≥3 1), menopausal status (premenopause and perimenopause 0/postmenopause 1), use of hormone replacement therapy in the last month (yes 1/no 0), history of fractures (yes 1/no 0), history of spine, hip, and/or forearm fracture after the age of 40 (yes 1/no 0), use of antiretroviral therapy (yes 1/no 0), hypothyroidism (yes 1/no 0), BMI (<25.0 0/≥25.0 1), TSH (normal 0/hypothyroidism or hyperthyroidism 1), free T4 (normal 0/abnormal 1)

EC estimated coefficient, *SD* standard deviation

in agreement with other studies [11, 13–16]. Nevertheless, there were no significant differences of BMD in the femoral neck in both groups as also reported by other authors [22, 23].

In the present study, low BMD at the lumbar spine and femoral neck was associated with the well-established risk factors of being postmenopausal, having a lower BMI and being white. Although most HIV-seropositive women were younger and premenopausal, which are protective factors for the occurrence of low bone mass, they also had a high prevalence of risk factors, because they were thinner and consumed more tobacco and alcohol than the control group. The results of our study emphasize the importance of evaluating the presence of traditional risk factors for the occurrence of osteopenia/osteoporosis [24, 25].

The influence of pregnancy on bone mass is not completely understood. We found that the number of pregnancies (≥3) was associated with higher BMD at the femoral neck. These data diverge from those of Allali et al., who found an association between a greater number of pregnancies and low bone mass, but no association with increased fracture risk compared with women with lower parity [26]. This can be explained, in part, by decreased bone mass due to the higher demand for calcium during pregnancy [25] and breastfeeding [27]. However, these data are controversial, because other studies have shown an increase in bone mass due to higher estrogen levels and increased bone overload in the third trimester [28–30]. Thus, the data are inconclusive regarding the effects of pregnancy and lactation on bone mass.

Multiple regression analysis showed a negative association between HIV infection and lower BMD at the lumbar spine but not at the femoral neck. Some authors report that HAART may lead to greater bone loss in the spine than in the femur, which could be attributed to differences in bone tissue type. The femur contains large amounts of cortical bone with few osteoclasts, while the vertebrae consist primarily of trabecular bone, which is rich in osteoclasts and have a higher metabolism [24, 31, 32]. In this study, over 90 % of HIV-seropositive women used HAART, which may explain the association between HIV-seropositive impaired BMD at the lumbar spine. However, there was no significant difference in the prevalence of low bone mass in the femoral neck within HIV-seropositive and HIV-seronegative female groups. This suggests that the use of antiretroviral therapy, when successful, prevents comorbidities related to HIV infection, like the occurrence of low bone mass.

The process involved in bone loss in HIV-seropositive women is complex and multifactorial. There are factors related to the infection itself, such as the occurrence of a chronic inflammatory process, with a direct action of the virus in the activation and differentiation of osteoblasts and in osteoclast inactivation [18]. The use of HAART and the presence of common risk factors associated with the aging process in HIV seropositive and seronegative women may also play a role [32, 33]. HIV-seropositive women may not have kept habits that favor the maintenance of bone density and quality, such as physical exercise and good eating habits. In addition, many women acquire HIV at a young age, which may impair the acquisition of peak bone mass [34–36].

This study has limitations. It is a cross-sectional study, so causal relationships cannot be attributed. There were differences between the groups of HIV seropositive and seronegative women that undermined the homogeneity of the samples; however, these differences were controlled for in the multivariate analysis. There is also the possibility of bias being present in some questions, which may have affected the answers of HIV-seropositive women as they may not have wanted to feel socially excluded. As a result, we may have underestimated some risk factors and environmental behaviors.

Conclusion

In this population, HIV-seropositive women, on long-term HAART and in good immunological conditions, exhibited BMD that is similar to non-infected women despite having lower weight and more likely to being addicted to alcohol and cigars. In the post-HAART era, there is an increasingly longer survival of infected HIV women. Thus, there is a

greater concern about comorbidities resulting from aging within the well-controlled HIV population like low bone mass. Therefore, it is important to identify not only factors inherent to the infection that may interfere with bone metabolism but also the traditional risk factors linked to osteoporosis. Few studies have addressed specific strategies for prevention of osteoporosis at the time of diagnosis of HIV infection and the beginning of HAART. The establishment of appropriate measures, both preventive and therapeutic, can help reduce the risk of fractures and their consequences in this group of HIV-infected women.

Conflicts of interest None

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