ORIGINAL ARTICLE

# NO EVIDENCE OF OSTEOPOROSIS IN YOUNG HTLV-1-INFECTED CARRIERS

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## Abstract

Osteoporosis has been reported among Human T-cell Lymphotropic Virus type 1 (HTLV-1) infected aged patients with HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) diagnosis. However, the association between osteoporosis and HTLV-1 infection remains unclear. This study aimed to evaluate the presence of bone disorders in young HTLV-1 asymptomatic individuals. A cross sectional study was carried out at the HTLV Reference Center in Salvador, Brazil. Forty-seven HTLV-1 infected asymptomatic and 108 healthy subjects aged between 20 to 45 years were included. Biochemical markers of bone metabolism were measured and bone mineral density (BMD) was determined at the femoral neck and at the lumbar spine ($L_1$-$L_4$). Significant low BMD (Z-score <-1 ) was found in HTLV-1 infected individuals (1.177 ± 0.103) compared to control subjects (1.225 ± 0.146). In logistics regression analysis HTLV-1 infected subjects were more likely to have low BMD (OR = 3.48; 95%CI 1.29- 9.43) adjusted for low education and body mass index (BMI). Osteoporosis (Z-score <-2) was not found among HTLV-1-infected group. In conclusion, our results found a low BMD in patients infected with HTLV-1 compared to uninfected controls. However, osteoporosis was not observed. Further studies should be conducted to evaluate the relationship between HTLV-1-infection and low BMD.

*Keywords*: HTLV-1; Bone mineral density; Osteoporosis.

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## INTRODUCTION

Human T-cell Lymphotropic Virus type 1 (HTLV-1) is endemic worldwide and it is estimated that 10 million people harbor the virus.[1] This virus is etiologically linked with adult T cell leukemia (ATL),[2] HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP),[3,4] uveitis[5] and infective dermatitis.[6] Several other diseases have also been associated with HTLV-1, such as polymyositis, synositis, thyreoiditis, bronchi alveolar pneumonia, indicating a multi-systemic involvement in this infection.[7] The city of Salvador, capital of Bahia State, located in the Northeast of Brazil has the highest prevalence of HTLV-1 infection in this country.[8] Through a population-based study, we have demonstrated that the overall prevalence of HTLV-1 in this city was 1.74%, increasing with age reaching 9.0 % in women aged 50 years and older.[9]

Previous studies have attempted to identify risk factors for bone disorders in retrovirus infection, mainly in HIV patients.[10,11] Osteoporosis associated with HTLV-1 has been reported in older symptomatic HAM-TSP patients with walking difficulties.[12]

In the present study, we evaluate the presence of bone disorders in young HTLV-1 asymptomatic individuals from Salvador that could constitute a complication of this infection.

## MATERIALS AND METHODS

### STUDY DESIGN AND POPULATION

An outpatient cross-sectional study was carried out between May and November 2005 at the HTLV-1 Reference Center of the Escola Bahiana de Medicina e Saúde Pública (EBMSP), Salvador, Bahia, Brazil. An inter-disciplinary project including medical care, laboratory diagnosis, psychological assistance and physiotherapy is being carried out in this center. HTLV-1-infected patients were selected consecutively. The HTLV-1 non-infected individuals were recruited among relatives of HTLV-1 infected individuals and among outpatients by a flyer posted at the EBMSP Medical Center. The inclusion criterion was to be aged between 20 and 45 years. The exclusion criteria were as follow: a) HAM/TSP diagnosis; b) treatment with steroids in the past 2 months; c) amenorrhea for more than 6 months or hypoestogenism indicated by 17b-OH-estradiol levels <20µg/ml; d) hormonal treatment including GH, thyroid hormone, testosterone, megestrol, or oxandrolone in the past year (estrogen/progesterone used for contraception was permitted); e) an underlying medical condition predisposing to osteoporosis, such as renal failure (plasma creatinine greater than 1.5 mg/dl); liver insufficiency (jaundice, ascites, encephalopathy, decreased serum cholesterol); clinical signs of hepatic cirrhosis; diabetes mellitus; previous diagnosis of other endocrine diseases; f) recent history of extended bed rest; g) previous diagnosis of metabolic bone disease; h) drug therapy that could interfere with bone metabolism (vitamin D, glucoconicoids, calcitonin, cytostatics, anticoagulants, diuretics, fluoride, lithium, or bisphosphonates) and h) patients who did not consent to participate in the study.

The HTLV-1 infection was assessed according to the algorithm recommended by the Brazilian Ministry of Health. Briefly, plasma samples repeatedly positive in duplicate by ELISA (HTLV-1/HTLV-2 Ab-Capture ELISA Test System, Ortho. Clinical Diagnostic Inc. Raritan, New Jersey, USA) were confirmed and discriminated between HTLV-1 and HTLV-2 using Western Blot (HTLV Blot 2.4; Genelabs, Singapore). Polymerase Chain Reaction (PCR) analysis was performed in samples with undetermined results.

All volunteers gave written informed consent before entering the research protocol. The Ethics Committee of EBMSP approved this study.

### DATA COLLECTION PROCEDURES

A standardized questionnaire was applied to all participants by a single interviewer to obtain the following data: age, sex, years of formal education, his-

tory of smoking, alcohol consumption, past medical history, current medication and current exercise level. No assessment of nutritional status of calcium intake was made. As Salvador's population is highly racially mixed, mainly of African and Portuguese descendants,[13] this leads to difficulties in classifying individuals according to ethnic groups and therefore we did not include race as a study variable.

## BIOCHEMICAL PARAMETERS OF MINERAL METABOLISM.

Ten ml of venous blood were obtained by venous puncture from patients who had not undertaken any vigorous exercise for 24 hours, fasted overnight, for 10 hours, but with free water intake (5ml were collected in a tube containing ethylenodiamine tetra acetic acid (EDTA) as anticoagulant and the other 5ml without anticoagulant). The serum samples were immediately processed in a routine laboratory. Aliquots of serum, plasma and dry blood containing cells were stored at –20°C.

Serum calcium, phosphorus magnesium, and total alkaline phosphatase activity were measured by the Autoanalyser Labmax 240 (Labtest Diagnóstica, São Paulo, Br). Osteocalcin levels were determined using a commercial kit (Osteocalcin, RIA DPC, 0.2 ng/ml, 6.1%, 11.3%). Hormones levels were evaluated using the following commercial assays: TSH, IRMA ( Bayer Gnost Behring, Germany); total thyroxine, RIA (DPC, coated tube, 0.3 mg/dl, 4.2%, 4.9%); free testosterone, RIA (Bayer, coated tube, 0.15 pg/ml. 4.0%, 5.5%); beta estradiol, RIA (DPC, coated tube, 8 pg/ml, 5.8%, 7.4%,).

## BONE MINERAL DENSITY (BMD) EVALUATION

The BMD (expressed in g/cm2) of each participant was measured by dual-energy x-ray absorptiometry of lumbar spine (L1-L4) and proximal femur. All measurements were performed by the same technician using the same densitometer (DPX-L; LUNAR, MADISON, WI, USA) under the supervision of a skilled radiologist of the EBMSP Medical Centre. All data were presented as absolute values or Z-score.

Low bone density was defined by a lumbar spine and/or proximal femur Z-score < -1.0 according to WHO recommendations.[14] The data were adjusted for age and gender and expressed as a Z-score. Body Mass Index (BMI) was calculated using standard formula (weight/height$^2$).

## STATISTICAL ANALYSES

Normal distribution of data was analyzed by the Kolmogorow-Smirnov normality test. Results are expressed as means ± standard deviations for continuous variables and compared by Student's t-test. Qui-square test with no continuity correction was used for analysis of proportions. Data that showed unequal variance or abnormal distribution were analyzed by Mann-Whitney rank sum test. In order to compare BMD and Z-scores distributions, four groups (HTLV positive (+) men, HTLV positive (+) women, HTLV negative (-) men and HTLV negative (-) women) were analyzed by the ANOVA test. All variables associated with low BMD ($p<0.20$) as well as those with biological plausibility were included in an exploratory multivariate model. Then, a stepwise backward procedure on multiple logistic regression models for computed adjusted estimates of the relationship between low BMD and HTLV-1 infection was used. The final model was carried out using the following variables: sex (male/female), years of formal education (≥10, <10 years), smoking (no, yes), alcohol consumption (no, yes), physical activity (yes, no) and BMI (≥25, <25 kg/m$^2$). Then we performed a multivariable analysis by formal education (≥10, <10 years) to estimate the association between HTLV-1 infection and BMD in these two groups because low education is associated with HTLV-1 infection and lower BMD. Epi Info for Windows®, version 3.3.2 was used for data entry and statistical analysis was performed using (SPSS, Inc. Chicago, IL) version 11.0. Differences of $p<0.05$ were considered statistically significant.

## RESULTS

One hundred sixty one individuals (51 HTLV-1--infected asymptomatic and 110 non-infected non infected individuals) all meeting the inclusion criterion were initially enrolled. Six out of 161 (3.72%) patients (4 HTLV-1 positive and 2 HTLV-1 negative) were excluded from the study due to low levels of 17b-OH-estradiol (<20µg/ml). Therefore, 155 individuals were included in this study, 47 (30.3%) HTLV-1 infected patients and 108 (69.7%) HTLV-1 non-infected controls.

The socio-demographic, densitometry and laboratorial characteristics of the individuals are presented in Table 1. HTLV-1 infected patients had fewer years of formal education and smoked more than non-infected controls. No case of anemia was found in HTLV-1 patients but one individual in the control group was identified as being anemic. Despite this, we observed lower significant differences in hemoglobin levels in the HTLV-1 infected group, though these levels were still within the normal range. In addition, mean corpuscular volume (MCV) values were normal and similar in both groups. A significantly lower number of leucocytes and relative segmented cells was observed in the HTLV-1 infected group. In addition, the relative number of lymphocytes as well as albumin levels were higher in HTLV-1 infected patients. Serum calcium osteocalcin, alkaline phosphatase, testosterone, and TSH levels were similar in both groups.

**Table 1.** Characteristics of 47 HTLV-1 carriers and 108 non-infected individual from Salvador, Brazil

| Characteristic | HTLV-1 Positive (N = 47) | HTLV-1 Negative (N = 108) | p-value |
|---|---|---|---|
| Age (years)* | 33.3 ffl 6.8 | 35.1 ffl 6.9 | 0.152 |
| Female (%) | 70.2 | 54.6 | 0.101 |
| Smokers (%) | 27.7 | 11.1 | 0.019 |
| Alcohol Ingest (%) | 72.3 | 74.1 | 0.979 |
| Physical Activity (%) | 44.7 | 31.5 | 0.163 |
| Formal Education <10y (%) | 42.6 | 21.3 | 0.012 |
| BMI (kg/m2)* & | 25.3 ffl 4.0 | 24.8 ffl 3.4 | 0.422 |
| BMD Spine (L1-L4)*& | 1.177 ffl 0.103 | 1.225 ffl 0.146 | 0.022 |
| BMD Hip*& | 1.078 ffl 0.143 | 1.084 ffl 0.143 | 0.794 |
| Hemoglobin (g/dl)* & | 13.44 ffl 1.03 | 13.97 ffl 1.50 | 0.013 |
| MCV (unid)* & | 85.51 ffl 3.94 | 86.75 ffl 5.23 | 0.149 |
| Leucometry (cels/mm3)* | 5,163.8ffl1,893.8 | 6,334.7ffl1,889.8 | <0.001 |
| Relative Segmented cells* | 51.93 ffl 10.84 | 56.92 ffl 10.18 | 0.013 |
| Relative Lymphocytes* & | 37.37 ffl 9.87 | 29.99 ffl 9.01 | <0.001 |
| Albumin* | 4.68 ffl 0.36 | 4.36 ffl 0.49 | <0.001 |
| AST* | 25.6 ffl 7.9 | 24,2 ffl 9.7 | 0.595 |
| ALT* | 23.9 ffl 20.7 | 23.6 ffl 14.5 | 0.299 |
| Alkaline Phosphatase* | 61.3 ffl 19.2 | 54.9 ffl 28.3 | 0.076 |
| Osteocalcin* | 5.31 ffl 3.23 | 5.42 ffl 2.71 | 0.591 |
| TSH* | 1.78 ffl 0.86 | 1.85 ffl 1.22 | 0.553 |

* Mean ffl SD; & Normal distribution, t-test performed; BMI: body mass index; BMD: bone mineral density MCV: mean corpuscular volume, AST ALT TSH

HTLV-1 infected individuals (15 out 47; 31.9%) had significantly lower BMD (Z score<-1) than not infected ones (12 out 108; 11.1%) at lumbar spine BMD (p=0.022,).). However, men and women with HTLV-1 had normal BMD at the hip (Table 2 and 3).

**Table 2.** Densitometry, Clinical, Laboratorial and demographics characteristics between 63 men HTLV-1 positive and negative

| Characteristic | HTLV-1 Positive (N = 14) | HTLV-1 Negative (N = 49) | p-value |
|---|---|---|---|
| BMD Spine (L1-L4)*& | 1.158(0.082) | 1.228(0.142) | 0.025 |
| BMD Hip*& | 1.121(0.146) | 1.137(0.158) | 0.731 |
| Age (years) * & | 34.7(6.9) | 33.9(6.0) | 0.677 |
| Smokers (%) | 14.3 | 12.2 | 0.840 |
| Alcohol Ingest (%) | 71.4 | 75.5 | 0.757 |
| Physical Activity (%) | 71.4 | 44.9 | 0.080 |
| Formal Education <10y (%) | 64.3 | 24.5 | 0.005 |
| BMI (kg/m$^2$)* & | 25.0(2.8) | 25.1(3.7) | 0.910 |
| Hematocrit (g%)* & | 42.16(2.45) | 44.25(3.20) | 0.028 |
| MCV (unid)* & | 86.29(3.17) | 87.91(4.98) | 0.254 |
| Leucometry (cels/mm3)* † | 4,500.0(2,324.1) | 6,429.8(1,851.2) | <0.001 |
| Relative Segmented cells* † | 49.41(12.78) | 52.20(16.27) | 0.272 |
| Relative Lymphocytes* & | 37.47(11.51) | 30.05(8.42) | 0.010 |
| Albumin (g/dl)* † | 4.79 (0.34) | 4.43(0.46) | 0.004 |
| Total Calcium (mg/dl) † | 9.23(1.78) | 9.58(0.96) | 0.817 |
| Phosphorus* & | 4.02(1.13) | 4.06(0.83) | 0.906 |
| Alkaline Phosphatase* & | 59.42 (19.22) | 62.62(31.38) | 0.720 |
| Osteocalcin*† | 6.10 (2.72) | 5.05 (2.45) | 0.074 |

*Mean(Standard Deviation). & T-test performed. † M-W performed.

**Table 3.** Densitometry, Clinical, Laboratorial and demographics characteristics between 92 women HTLV-1 positive and negative

(to be continued)

| Characteristic | HTLV-1 Positive (N = 33) | HTLV-1 Negative (N = 59) | p-value |
|---|---|---|---|
| BMD Spine (L1-L4)*& | 1.185(0.111) | 1.222(0.151) | 0.224 |
| BMD Hip*& | 1.059(0.139) | 1.041(0.114) | 0.482 |
| Age (years) * & | 33.0(7.2) | 35.3(7.0) | 0.139 |
| Smokers (%) | 5.1 | 12.1 | 0.222 |
| Alcohol Ingest (%) | 72.9 | 72.7 | 0.987 |
| Physical Activity (%) | 20.3 | 33.3 | 0.167 |
| Formal Education <10y (%) | 18.6 | 33.3 | 0.113 |
| BMI (kg/m$^2$)* & | 25.4(4.5) | 24.4(3.1) | 0.302 |
| Hematocrit (g%)* & | 39.84(2.96) | 40.63(3.82) | 0.307 |
| MCV (unid)* & | 85.18(4.23) | 85.78(5.27) | 0.578 |
| Leucometry (cels/mm3)* & | 5,445.5(1,639.0) | 6,255.7(1,933.5) | 0.045 |

**Table 3.** Densitometry, Clinical, Laboratorial and demographics characteristics between 92 women HTLV-1 positive and negative (conclusion)

| Characteristic | HTLV-1 Positive (N = 33) | HTLV-1 Negative (N = 59) | p-value |
|---|---|---|---|
| Relative Segmented cells* † | 53.00(9.93) | 58.00(9.73) | 0.020 |
| Relative Lymphocytes* & | 37.32(9.29) | 29.95(9.54) | 0.001 |
| Albumin (g/dl)* † | 4.63 (0.36) | 4.31(0.51) | <0.001 |
| Total Calcium (mg/dl) & | 9.44(0.80) | 9.41(0.97) | 0.889 |
| Phosphorus* & | 3.78(0.85) | 4.12(0.86) | 0.078 |
| Alkaline Phosphatase* † | 62.10 (19.41) | 48.46(23.93) | 0.003 |
| Osteocalcin* † | 4.97 (3.41) | 5.73 (2.90) | 0.089 |

*Mean (Standard Deviation). & T-test performed. † Mann-Whitney performed.

In the multivariate analysis, the association between low BMD and HTLV-1 infection remained statistically significant (OR 3.48; CI 95% 1.29-9.43) adjusting for low education, BMI (Table).

**Table 4.** Odds ratios for the two exploratory models with variables associated to Low BMD in the spine, in Salvador, Bahia, Brazil

| Variable | ss | OR | 95% CI |
|---|---|---|---|
| Model 1[a]<br>HTLV-1 positive | 1.42 | 4,14 | 1.41 - 12.21 |
| Low education (< 10 y) | 1.80 | 6.07 | 2.12 - 17.34 |
| Female | -0.06 | 0.94 | 0.31 - 2.88 |
| Smoker (Current or former) | -0.71 | 0.49 | 0.12 - 2.10 |
| Physical Activity (yes) | -0.19 | 0.82 | 0.27 - 2.46 |
| Age (years) | 0.01 | 1.01 | 0.94 - 1.09 |
| BMI (kg/m$^2$) | -0.25 | 0.76 | 0.67 - 0.90 |
| Model 2[b]<br>HTLV-1 positive | 1.35 | 3.86 | 1.38 - 10.80 |
| Low education (< 10 y) | 1.81 | 6.09 | 2.15 - 17.27 |
| Female | -0.03 | 0.97 | 0.34 - 2.74 |
| Age (years) | 0.01 | 1.01 | 0.94 - 1.09 |
| BMI (kg/m$^2$) | -0.25 | 0.78 | 0.69 - 0.90 |

[a,b]BMI and age were described with continuous;

Since low levels of education are associated with osteoporosis, we evaluated the relationship between low BMD and the variables in the final logistic regression model, stratified by formal education (Table 5). Then, we observed that the association between low BMD and HTLV-1 remained significant only in the individuals who had more than 10 years of education (OR 13.1; 95% CI 2.42 – 70.89).

**Table 5.** Factors associated of Low BMD in Salvador, Bahia, Brazil, stratified by educational levels.

| Variable | Low Education (< 10 y) | Better education (· 10 y) |
|---|---|---|
| | OR (95% CI) | OR (95% CI) |
| HTLV-1 positive | 1.33 (0.33 – 5.36) | 11.48 (2.30 – 57.37) |
| Female | 0.78 (0.19 – 3.15) | 0.98 (0.16 – 5.96) |
| Age* | 1.02 (0.92 – 1.12) | 1.00 (0.89 – 1.01) |
| BMI (kg/m$^2$)* | 0.78 (0.63 – 0.95) | 0.80 (0.63 – 1.01) |

* BMI and age were described with continuous.

## DISCUSSION

We demonstrated that young HTLV-1 infected man have a low BMD compared to uninfected controls. Indeed, those subjects were 3.5 times more likely to have low BMD than healthy controls, however no evidence of osteoporosis was found. To our knowledge, this is the first report on low BMD among asymptomatic HTLV-1 carriers.

The differences found between HTLV-1 infected and non-infected individuals such low leucometry and higher relative lymphocytosis could be related to the laboratorial profile of the viral infection. In addition, more smoking and lower formal education could be related to socio-economic conditions. Indeed HTLV-1 infection is associated with low levels of education and income[9] that are also associated with more smoking.[15] Therefore, we could hypothesize that in these low educated individuals, the calcium ingested was not satisfactory since low levels of education are a proxy for low socio-economic levels. Association between lower socioeconomic conditions and calcium intake was described previously.[16]

However, after logistic regression, HTLV-1 infection remained significantly associated with low BMD in more educated individuals. This fact could suggests that the virus infection play a role in bone mineral metabolism. We did not find significant differences of osteocalcin levels between carriers and not infected individuals although we observed higher rates in HTLV positive group and the same trend in males. This fact could reflect a high bone turnover. Increased osteocalcin levels may be useful in predicting which osteopenic woman will progress to osteoporosis in the spine, independently of age and body size at baseline.[17]

We observed low BMD in HTLV-1- infected men compared with non-infected controls but this difference was not found in HTLV-1-infected women. Both osteoporosis and HTLV-1 infection are more frequent in women and the risk of developing both conditions increases with age.[9,18] Estrogen is a protective factor for osteoporosis.[17] Moreover, estradiol levels are usually lower in men than women of the same age. This higher prevalence of low BMD in HTLV-1-infected men could be explained by a possible synergism between HTLV-1 and lower estrogen levels. This fact strengthens the hypothesis of an association between HTLV-1 infection and alterations in bone mineral metabolism.

We do not know yet how HTLV-1 infection interferes with bone mineral metabolism, leading to bone demineralization. Several hypotheses could be raised. First, sexual hormones, such as estradiol and testosterone, and PTH levels could interfere in bone turnover in these individuals.[20] However, we observed normal levels of estradiol and testosterone in women and men respectively. Moreover, increased serum levels of parathyroid hormone related peptides ($PTH_RP$) were described in ATL and HAM/TSP patients as well as in

asymptomatic carriers.[21-23] We did not measure biochemical markers of bone resorption neither PTH levels. Thus, further studies need to be done to better evaluate the role of hormones in low BMD. Secondly, several cytokines and growth factors seem to be involved in the modulation of osteoblasts and osteoclasts and could be related to the virus effects.[24] These cytokines may be produced mainly by CD4+ T-lymphocytes in response to HTLV-1 stimulation.[24] Moreover, previous studies demonstrated that the viral protein Tax could play an important role in bone pathogenesis inducing multiple cytokines genes, such as IL-6, TNF.-α, as well as GM-CSF, that modulate osteoclasts and increase bone resorption.[25] Furthermore, Tax induces cytokines to modulate the production and the degradation of intracellular matrix enzymes metalloproteinase in osseous tissues. This effect could lead to pathological deregulation of bone extra-cellular matrix proteins that together with other host factors could contribute to the low BMD observed in HTLV-1 patients.[12,26] However, in our study we were not able to measure cytokines levels. Finally, as BMD appears to be under genetic control, another possibility could be a genetic vulnerability. The variation in the regulatory region of the IL-6 gene may affect bone metabolism and lead to variations in BMD.[28-34] Moreover, polymorphisms in the IL-6 promoter region have also been associated with different cytokine levels.[27] We have recently observed that the -174G/C was associated with lower osteocalcin levels and HTLV-1 proviral load in the healthy HTLV-1 carriers, suggesting that this polymorphism could be involved in the pathology.[35]

In conclusion, we observed that infected man with HTLV-1 have lower BMD compared with non-infected controls of the same age. Yet, men and women with HTLV-1 had normal BMD at the hip. Further studies, especially longitudinal studies, should be conducted to understand the relationship between HTLV-1 infection and low BMD.

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