ORIGINAL REPORT

Evaluation of Bone Mineral Density in Iranian HIV/AIDS Patients

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Abstract- Bone disorders have emerged as a worrisome complication in HIV-infected patients in recent years. It is not clear that HIV infection itself or antiretroviral treatment or both are causes of bone loss. However, most studies have found a high prevalence of osteopenia and osteoporosis in HIV/AIDS patients. The objectives of this study were to determine the prevalence of osteopenia and osteoporosis in HIV-infected patients either untreated or receiving Highly Active Antiretroviral Therapy as compared with HIV negative persons. We also assessed the factors associated with these conditions. Bone Mineral Density was assessed by Dual Energy X-Ray Absorptiometry scans at the hip and lumbar spine in 36 AIDS patients receiving antiretroviral therapy and 44 HIV infected patients not receiving antiretroviral therapy (naïve patients) and 40 HIV negative individuals as control. Factors that affect BMD were also determined. Prevalence of osteopenia or osteoporosis in different regions was significantly higher in HIV/AIDS patients compared with HIV negative subjects (77.3% in HIV positive naïve patients, 86.1% in HAART-treated patients and 60% in the control group, P=0.002). Mean serum alkaline phosphatase was higher in HIV/AIDS patients than the control group (P=0.003). Osteopenia and osteoporosis in HIV-infected patients were associated with duration of HIV infection (P<0.0001) and antiretroviral treatment (P=0.012). Prevalence of osteopenia and osteoporosis in HIV/AIDS patients was higher than HIV negative individuals. Osteopenia and osteoporosis in HIV/AIDS patients was associated with duration of HIV infection and antiretroviral treatment.

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Introduction

Nowadays, along with improving HIV/AIDS patients' survival and introduction of several potent antiretroviral drugs, the mortality and morbidity of HIV/AIDS has had significant reduction (1,2), although new problems due to HIV infection and adverse effects of antiretroviral drugs have been encountered (3-6). One of these problems is metabolic bone disorders. Bone disorders have emerged as a worrisome complication in HIV-infected patients in recent years. It is not clear that if HIV infection itself or antiretroviral treatment or both are causes of bone loss; however, most of the studies have shown a high prevalence of osteopenia and osteoporosis in HIV/AIDS patients. Although skeletal fractures associated with osteoporosis are currently uncommon in HIV positive individuals, but they can be debilitating and potentially life–threatening and affect the quality of life in these patients (4-17).

Biochemical markers of bone turnover such as bone-specific alkaline phosphatase and osteocalcine in serum and urine samples are also useful for evaluating the risk of reduction of bone mineral density and response to treatment of osteoporosis (18). Hyperthyroidism and other endocrine disorders, hematologic disorders, genetic factors, gastrointestinal diseases such as celiac and inflammatory bowel disease, rheumatoid arthritis, hypogonadism, depression, alcoholism, renal and cardiac failure can cause secondary osteoporosis. Corticosteroids, insufficient intake of calcium and vitamin D, smoking, high level of cytokines in serum, sub optimal BMD in childhood and adolescent and race also contribute to osteopenia and osteoporosis (19-21). The objectives of our study were to estimate

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the prevalence of osteopenia and osteoporosis in AIDS patients receiving HAART, and HIV-infected patients not receiving antiretroviral drugs, in comparison with HIV negative controls and to assess factors associated with osteopenia or osteoporosis in HIV/AIDS patients.

Materials and Methods

Patients' selection

We enrolled HIV/AIDS patients who had referred to the Counseling Center for Behavioral Sciences at Imam Khomeini Hospital (Tehran University of Medical Sciences, Tehran, Iran) from March 2006 to March 2007. Criteria for inclusion were age over 18 and less than 65 years and serum positivity for HIV (positive Western Blot). Patients with any condition that could cause loss of BMD, such as menopause, history of hypogonadism, thyroid or parathyroid diseases, renal failure, prior administration of corticosteroids or anticonvulsant drugs, calcium, vitamin D, prolonged bed rest, major infectious diseases or neoplasm during the 6 months prior to the study were excluded. In this manner, 80 HIV positive patients were enrolled in this cross-sectional study. All of them agreed to participate in the study and signed an informed consent. First, socio-demographic and clinical data including age, gender, history of caffeine and alcohol intake, date of the first HIV positive test, medication history (including type and duration of all antiretroviral therapy and past use of any medications that may potentially alter bone metabolism), infection with hepatitis B & C, smoking, regular exercise, history of intra-venous drug use and past history of being a prisoner were recorded in a questionnaire. Anthropometric data including body mass index (BMI) was measured.

Then we chose 40 matched HIV negative individuals (with respect to age, gender, infection with chronic viral hepatitis B and C, alcohol and caffeine intake, and intra-venous drug use) and repeated the above mentioned steps for them. Generally, we tried to choose these controls among friends and family members of our HIV positive patients, so HIV negative subjects in this study were very similar to HIV positive patients regarding socio-economic status, diet and habits.

We divided our participants into three groups: HIV infected individuals not receiving HAART (naïve group), AIDS patients receiving HAART (AIDS group) and HIV negative individuals (control group)

BMD measurement and definitions of osteopenia and osteoporosis

In all of the participants, bone mineral density (BMD) was measured. We used Dual Energy X-Ray Absorptiometry scanner (DEXA) (Lexxos, France) to determine bone mineral density in right and left hip and lumbar spine (L1-L4) regions. World Health Organization (WHO) has devised four diagnostic categories related to bone demineralization: normal, osteopenia, osteoporosis and established osteoporosis with fragility fractures. The classification relies on DEXA scanning to determine bone density. Regional DEXA scans of hip and spine are used to assess bone density. DEXA results are reported in absolute terms, g/m^2, and relative terms, T-score and Z –score. The T –score is the number of standard deviations (SD) between the obtained result and the value expected in young individuals (25-30 years).The Z-score represents the number of standard deviations between the obtained result and an aged- matched average value from healthy individuals. Osteopenia is a T–score between 1 SD and 2.5 SD below the average found in young people. Osteoporosis is a T-score lower than 2.5 SD below the average found in young people. Established osteoporosis is a T-score lower than 2.5 SD in the presence of fragility fractures (22-26).

Laboratory tests

Some bone markers (serum calcium, phosphorus, alkaline phosphatase) were measured in all patients. CD4 count and serum albumin were also measured. Serum calcium levels with normal reference intervals 8.6-10.3 mg/dl, serum phosphorus levels with normal reference intervals 2.5-5 mg/dl, serum alkaline phosphatase levels with normal reference intervals 80-306 IU/L, serum albumin levels with normal reference intervals 3.5-5.5 g/dl were measured. CD4+ cell counts were determined by standard flow cytometry.

Statistical analysis

Statistical analysis was performed using SPSS, version 13 (SPSS Inc., Chicago, IL, USA). We used one way ANOVA and post Hoc Tukey tests for comparing means between groups if the distributions were normal. χ^2 test for independent proportions and Fisher's exact test were also used. Multiple logistic regression analysis was used to analyze the joint effect of the independent variables on osteopenia and/or osteoporosis.

Results

Characteristics of the 120 patients studied

The main characteristics of the 120 participants in the study are shown in Table 1. Of 80 HIV positive patients, 44 patients (36.7%) had never received antiretroviral therapy (naïve group) and 36 patients (30%) were taking HAART. The mean age in the AIDS group, naïve group and control group were 39.3 (24 -58 years), 34.9 (25 - 51 years) and 36.5 years old (20 - 62 years) respectively. In the naïve group, 37 (84.1%) men and 7 (15.9%) women were enrolled while in the AIDS group, 27 (75%) men and 9 (25%) women were included. In the HIV negative control group, 31 (77.5%) men and 9 (22.5%) women were enrolled.

Of 120 individuals enrolled in the study, 70 (58.3%) were smokers (77.2%, 38.9%, and 55%, in naïve, AIDS and control group, respectively). Eleven (9.2%) had alcohol intake regularly (at least 3 ounces per week) of those, 4 were naïve, 3 AIDS and 4 in the control group. Twelve patients reported regular consumption of caffeine (10% of all cases), among them, 2 were in the naïve, 5 in the AIDS and 5 in the control group.

Table 1. Summary of the main characteristics of 120 studied subjects (AIDS, naïve and control groups)

Variables	AIDS group (n=36)	Naïve group (n=44)	Control group (n=40)	*P*-value
Age, mean years ± SD	39.4±7.7	34.9±7.3	36.6±10.5	0.079
Male sex, n (%)	27 (75%)	37 (84.1%)	31 (77.5%)	0.579
Body mass index mean kg/m^2 ± SD	22.7±3.4	22.7±3.3	22.8±3.4	0.987
Marital status, n (%)				
Single	15 (41.7%)	19 (44.2%)	20 (50%)	
Married	16 (44.4%)	12 (27.9%)	18 (45%)	0.133
Divorced	3 (8.3%)	8 (18.6%)	2 (5%)	
Widow/ widower	2 (5.6%)	4 (9.3%)	-	
Educational level, n (%)				
Illiterate	1 (2.8%)	-	1 (2.5%)	
Primary school	7 (19.4%)	10 (22.7%)	6 (15%)	0.052
Secondary school	17 (47.2%)	17 (38.6%)	8 (20%)	
College	7 (189.4%)	13 (29.5%)	12 (30%)	
University	4 (11.1%)	4 (9.1%)	13 (32.5%)	
Smoking, n (%)	14 (38.9%)	34 (77.2%)	22 (55%)	0.005
Alcohol, n (%)	3 (8.3%)	4 (9.1%)	4 (10%)	0.969
Exercise, n (%)	7 (19.4%)	7 (15.9%)	9 (22.5%)	0.738
Coffee, n (%)	5 (13.9%)	2 (4.5%)	5 (12.5%)	0.301
HBV infection, n (%)	3 (8.3%)	6 (13.6%)	7 (17.5%)	0.499
HCV infection, n (%)	20 (55.6%)	32 (72.7%)	20 (50%)	0.085
Risk factor				
IV drug user, n (%)	16 (44.4%)	33 (75%)	16 (40%)	0.002
Sexual, n (%)	15 (41.7%)	14 (31.8%)	-	0.0001
Transfusion, n (%)	7 (19.4%)	-	-	0.0001
Prison, n (%)	14 (38.9%)	28 (66.7%)	6 (15.4%)	0.0001
Duration of HIV infection mean months ± SD (median)	55.6±54.6 (31.5)	23.1±18.2 (23)	-	0.002
CD4$^+$ T cell count mean cells/mm^3 ± SD (median)	268.7±184.9 (252)	423.6±239.1 (364)	-	0.002
CDC stage for HIV infection				
1	3 (8.3%)	14 (31.8%)	-	
2	17 (47.2%)	23 (52.3%)	-	0.004
3	16 (44.4%)	7 (15.9%)	-	

Note: CDC classification system for staging HIV/AIDS infection, based on CD4 count: stage 1:CD4≥500, Stage 2: 499≥CD4≥200 cell/ ml and stage 3:CD4<200.

Table 2. Mean of BMD in right & left hip and lumbar spine regions in 120 subjects

	Sub groups	mean	*P*-value
Right hip	Naïve (n=44)	0.919± 0.109	0.270
	AIDS(n=36)	0.875±0.200	
	Control(n=40)	0.930±0.137	
Left hip	Naïve (n=44)	0.945±0/121	0.175
	AIDS(n=36)	0.910 ±0.158	
	Control(n=40)	0.967±0.117	
Lumbar spine	Naïve n=44)	0.970± 0.119	0.326
	AIDS(n=36)	0.946± 0.173	
	Control (n=40)	0.955± 0.122	

Among 120 individuals enrolled in the study, 77 (64.2%) had chronic viral hepatitis .Five patients had hepatitis B, 61 patients had hepatitis C and 11 patients had both hepatitis B and C. Of 77 cases with concurrent hepatitis, 32 (72.2%) were in the naïve, 20 (55.6%) were in the AIDS and 25 (62.5%) were in the control group.
Among 80 HIV/AIDS patients, the average number of CD4 count was 353.9 cell/ml (20-1143 cell/ml). Average duration of HIV infection in 44 patients in the naïve group was 23.1 months and in 36 AIDS patients it was 55.6 months. The duration of HIV infection is significantly higher in patients receiving HAART than in patients in the naïve groups (*P*=0.002). We used multivariable statistical analysis for eliminating this confounding factor. In 36 AIDS patients, the mean time that the patients were exposed to NRTI (Nucleoside Reverse Transcriptase Inhibitor), NNRTI (Non Nucleoside Reverse Transcriptase Inhibitor) and PI (Protease Inhibitor) was 33.06 months, 0.26 month and, 26.8 months, respectively.

Prevalence of osteopenia and osteoporosis

Summary of BMD in the 3 studied groups has been shown in Table 2.

In all 120 patients, 50 cases (41.6%) showed evidence of decreased bone mineral density in right hip, 62 patients (51.6%) in left hip and 71 patients (59.1%) in lumbar spine. Cases of osteoporosis were exclusively in naive and AIDS groups (Table 3).

The prevalence of osteopenia and osteoporosis in right hip in 80 HIV/AIDS patients was similar to 40 HIV negative individuals in the control group (42.5% vs. 40%, *P*=0.793).The prevalence of osteopenia and osteoporosis in the left hip in 80 HIV/AIDS patients was higher than the HIV negative control group (55% vs. 45%), and the difference was not statistically significant (*P*=0.301). The prevalence of osteopenia and osteoporosis in the lumbar spine in 80 HIV/AIDS patients was higher than the HIV negative control group (62.5% vs. 47.5%), but the difference was not statistically significant (*P*=0.117).

Table 4 shows the prevalence of osteopenia in the hip and /or lumbar spine in AIDS and naïve patients and control subjects as 61.1%, 68.2% and 60%, respectively. Twenty five percent of AIDS patients and 9.1% of naïve patients were osteoporotic. Prevalence of osteopenia and osteoporosis in the hip and /or lumbar spine in HIV/AIDS were significantly higher than the control group (*P*>0.002).The mean serum calcium, albumin and phosphorus were similar in the 3 studied groups, but serum alkaline phosphates was higher in the control group (*P*>0.003).

Table 3. Prevalence of osteopenia and osteoporosis in the 3 studied groups in the right and left hip and lumbar spine

	Sub groups	Osteopenia	Osteoporosis	*P*-value
Right hip	Naïve (n=44)	18(40.9%)	0	0.126
	AIDS (n=36)	13 (36.1%)	3 (8.3%)	
	Control(n=40)	16 (40%)	0	
Left hip	Naïve (n=44)	21(47.7%)	2 (4.5%)	0.245
	AIDS (n=36)	17(47.2%)	4 (11.1%)	
	Control(n=40)	18(45%)	0	
Lumbar spine	Naïve (n=44)	24(54.5%)	2 (4.5%)	0.079
	AIDS (n=36)	19(52.8%)	5 (13.9%)	
	Control(n=40)	19(47.5%)	0	

Table 4. Laboratory and DEXA scanning characteristics for 120 studied subjects (AIDS, naïve and control groups)

Variables	AIDS group (n=36)	Naïve group (n=44)	Control group (n=40)	*P*-value
Plasma calcium level mean mg/dl ± SD	9.73±0.9	9.72±0.7	9.7±0.6	0.981
Plasma phosphorous level, mean mg/dl ± SD	3.6±1.3	3.3±0.4	3.5±0.5	0.079
Plasma alkaline phosphatase mean mg/dl ± SD	230.9±73.3*	225.1±63.4	183.9±58.8	0.003
Osteopenia, n (%)	22 (61.1%)	30 (68.2%)	24 (60%)	0.002
Osteoporosis, n (%)	9 (25%)	4 (9.1%)	-	

Relationship between BMD and other factors

We used the linear logistic regression model to eliminate the effect of confounding factors and determine factors that affect bone mineral density. We chose osteopenia and osteoporosis of hip and/or lumbar spine as dependent variable and age, sex, smoking, consumption of alcohol, exercise, HIV infection, chronic hepatitis B &C, BMI, intra-venous drug use (IDU) and history of being a prisoner as independent variables. HIV infection was associated with the presence of osteopenia and osteoporosis of hip and/or lumbar spine. (Unadjusted odd's ratio=2.889, CI 95% 1.240-6.731) (Table 5).

In HIV positive patients, duration of HIV infection and antiretroviral therapy were in association with osteopenia and osteoporosis (P<0.0001, P=0.012) respectively. There was no association between plasma alkaline phosphatase or $CD4^+$ T cell count with osteopenia and osteoporosis (Table 6).

Table 5. Association between the presence of osteopenia or osteoporosis at spine and/or hip and independent variables (risk factors)

Parameters	Osteopenia or Osteoporosis	
	Unadjusted odds ratio (CI95%)	Adjusted odds ratio (CI 95%)
Age (per year)	1.039 (0.988-1.093)	1.035 (0.980-1.093)
Gender (female)	1.473 (0.563-3.857)	2.971 (0.652-13.542)
Body mass index (per Kg/m^2)	1.032 (0.911-1.170)	1.027 (0.885-1.192)
Smoking	0.969 (0.424-2.218)	1.189 (0.297-4.759)
Alcohol	0.922 (0.229-3.719)	0.717 (0.145-3.537)
Exercise	0.984 (0.349-2.772)	1.087 (0.342-3.453)
HBV infection	0.733 (0.233-2.308)	1.203 (0.263-5.497)
HCV infection	1.114 (0.486-2.557)	0.908 (0.171-4.822)
IV drug user	0.964 (0.424-2.191)	0.329 (0.059-1.836)
Prison	1.769 (0.725-4.316)	1.877 (0.475-7.415)
HIV infection	2.889 (1.240-6.731)	2.384 (0.725-7.834)

Table 6. Relationship between HIV infection parameters and BMD finding (osteopenia, osteoporosis and normal) in HIV/AIDS patients.

Variables	Osteopenia (n=52)	Osteoporosis (n=13)	Normal (n=15)	*P*-value
Duration of HIV infection mean months ± SD	32.9±35.6	78.7±66.7	19±13.2	<0.0001
Duration of antiretroviral therapy mean months ± SD	11.7±26.3	41.1±70	3.1±5.9	0.012
Plasma Alkaline phosphatase mean mg/dl ± SD	222.1±69.5	236.4±65.6	239.8±64.9	0.595
$CD4^+$ T cell count mean cells/mm^3 ± SD	360±218.3	319.7±267.7	359.6±241.9	0.844

Discussion

The first report of prevalence of osteopenia and osteoporosis in HIV/AIDS patients was in 1999, when Ireland and Romeyn reported that among 20 HIV positive men with CD4 cell counts around 100 cell/cm^3 or less, 9 (45%) had evidence of osteopenia and 8 (40%) were diagnosed with osteoporosis (85% had osteopenia or osteoporosis). Among 8 patients with CD4 counts above 100 cell/cm^3, 7 (87%) showed osteopenia and 1(13%) showed osteoporosis. (100% had osteopenia or osteoporosis) (8). In our study, in 80 HIV/AIDS patients, 65% showed osteopenia and 16.2% showed osteoporosis (81.2% osteopenia or osteoporosis in HIV/AIDS patients). So, the prevalence of osteopenia and osteoporosis is also high in our patients.

In the 8th Conference on Retroviruses and Opportunistic Infection (CROI) in February 2001, at least 15 abstracts and posters focused on bone mineral disorders in HIV/AIDS patients. According to those reports, prevalence of osteopenia in the lumbar spine was 21-45% (10-13), but in our study the prevalence of osteopenia in the lumbar spine was higher (52.8%) in HIV/AIDS patients.

Several recent studies have found a high rate of bone mineral loss in HIV positive persons who have never taken anti-HIV drugs. The majority of these studies suggested that persons treated with HAART were not more likely to experience osteopenia than those who were antiretroviral naïve (9-13). For example, Lawal and colleagues found equivalent rates of reduced BMD in a cohort of 36 HIV positive men assessed in 1993 (pre HAART) and a cohort of 22 HIV positive, HAART-treated subjects in 1998 (13). Our study showed equivalent rates of reduced BMD in HAART–treated and naïve patients.

Knobel and colleagues (2001), compared 80 HIV positive patients (26 naïve, 37 on HAART containing PI, 17 on HAART without PI) with 100 age and sex matched HIV negative individuals (as control group), with respect to BMD using DEXA scanning in the lumbar spine and proximal femur. In that study, no difference was found between HIV positive groups. However, HIV positive patients had reduced bone mineral density in comparison with HIV negative control group in both lumbar spine and femur. Mean of BMD in the HIV negative control group, for the lumbar spine was 1.064 g/m^2 and in HIV positive patients it was 0.987 g/m^2 (SD=±0.120 g/m^2). $CD4^+$ T cell counts and duration of therapy had no association with BMD, but BMD was only associated with BMI (r=0.3, P=0.02).Treatment with PI was associated with reduced BMD in the femur. Twenty five percent of individuals in the control group and 67.5 % of HIV positive patients were osteopenic. Five percent and 21.2% of them were osteoporotic, respectively (11). In contrast, in our study, the prevalence of osteopenia and osteoporosis in HIV positive groups was similar to the HIV negative control group, but duration of infection and administration of HAART were in association with reduced bone mineral density in the lumbar spine (P<0.0001, P=0.012 respectively). We found no association between BMD and BMI or CD4 T cell counts.

Gowan measured BMD in 251 HIV positive patients using DEXA scanning and found that 24% were osteopenic and 1% was osteoporotic (10). Osteopenia and osteoporosis in our study is higher than in Gowan's study.

Tebas enrolled 122 individuals in his study: Sixty four patients on HAART (containing PI), 22 patients as control group and 36 HIV-infected patients not receiving PI. The PI-treated group had 104 weeks median duration of treatment and had a higher mean age than the two other groups (41 years vs. 33-37 years, P=0.001). DEXA scanning of the lumbar spine and proximal femur was performed to determine bone mineral density. Fifty percent of the HAART group was osteopenic. Twenty one percent of the HAART group patients were osteoporotic (P=0.02), compared with 6% in the control group and 11% of HIV positive patients not receiving PI (18). The prevalence of osteopenia and osteoporosis in HAART-treated patients in our study were 61.1% and 25%, respectively in hip and/or lumbar spine. Prevalence of osteoporosis in naïve patients in our study was 9.1% in hip and/or lumbar spine. In the HIV negative control group none of the participants were osteoporotic.

Anastos measured bone mineral density in 88 HIV negative and 184 HIV positive patients (90 patients not on HAART, and 94 patients on HAART). BMD was 6-8% lower in the HIV positive than in the HIV negative patients (P<0.03), with similar BMD in the HIV positive patients irrespective of receiving HAART. The prevalence of osteopenia and osteoporosis was 6.4% in HIV negative patients, 18.9% in HIV positive patients not on HAART and 20.4% in HIV positive patients receiving HAART (adjusted OR=3.15, P=0.027 in all HIV positive vs. HIV negative patients) (15). The prevalence of osteopenia and osteoporosis in Anastos' study is lower than our study. Moore conducted a study on 72 HIV positive patients. The prevalence of osteopenia and osteoporosis in his study was 50-

66%.The mean age of his patients was 39 years, 35% were smokers and the mean time since HIV diagnosis was 4.9 years. Sixty-six percent had taken antiretroviral therapy. In this study, the history of antiretroviral therapy was associated with reduced bone density (OR=3.08, *P*=0.05) (9). In our study, the prevalence of osteopenia and osteoporosis in HIV positive patients was also high, and the mean age of our patients was 39.39 years old in HAART-treated patients and 34.95 years old in naïve patients. Sixty percent were smokers and the mean time since HIV diagnosis was 55.6 months in HAART-treating patients and 23.1 months in naïve patients. Duration of HIV infection and HAART were in association with decreased bone mineral density.

We observed a high prevalence of osteopenia and osteoporosis in our HIV/AIDS patients. This high prevalence was associated with duration of HIV infection and receipt of HAART. Screening of all HIV/AIDS patients and treatment of osteoporotic patients are recommended. Screening should include a baseline DEXA measurement of BMD as well as annual BMD monitoring. Patient education regarding intake of sufficient amounts of calcium and vitamin D throughout life, regular weight-bearing exercise and avoidance of use of tobacco and alcohol intake are also recommended.

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