Research Article

Prevalence of low bone mineral density in Human Immunodeficiency Virus-infected patients and its correlation with other determinants

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ABSTRACT

Background: The patients infected with human immunodeficiency virus (HIV) are potentially at risk of low bone mineral density (BMD). The present study was done to find out the prevalence of low BMD in HIV-infected patients and its correlation with other factors such as gender, body mass index (BMI), CD4 count, and highly active antiretroviral therapy (HAART). **Methods:** This was an observational cross-sectional study conducted in a tertiary care center for 1 year period. A total of 127 HIV-infected patients were evaluated for BMD by dual-energy X-ray absorptiometry (DEXA) scans at two sites lumbosacral spine and bilateral neck femur. Correlation with other factors was also studied. **Results:** The diagnosis of low BMD was established in 105 (82.67%) patients. Osteoporosis (44.1%) was more common than osteopenia (38.6%) at the lumbosacral spine. The mean T score of the DEXA lumbar spine and bilateral neck femur was observed to be −2.113 and −1.379, respectively. Males (88.73%) had low BMD than females (75%). Approximately 94.5% of subjects having BMI <18 had low BMD in contrast to 80.8% among subjects having BMI >18. After treatment, 47 patients had CD4 count <400 and 80 > 400. Forty-three patients out of 47 (91.5%) had low BMD and 62 out of 80 (77.5%) had low BMD. **Conclusion:** Low BMD is prevalent in HIV-infected subjects. Low BMI, persistently low CD4 count, tenofovir containing HAART regimen showed a positive correlation with low BMD. Hence, HIV infection should be considered as a risk factor for bone disease.

Key words: *Body mass index, CD4 count, Human immunodeficiency virus, Osteoporosis*

Human immunodeficiency virus (HIV) infection is a major global health problem. According to the World Health Organization (WHO), there were approximately 36.7 million (34.3–39.8) people living with HIV at the end of 2016 with 1.8 million (1.9–2.2) people becoming newly infected with HIV in 2016 globally and about 5000 new infections per day [1]. India currently has an estimated 2.1 million people living with HIV (PLHIV), the third highest globally after South Africa and Nigeria [2]. The global prevalence of people living with HIV has increased more than 4-fold since 1990, reflecting the combined effects of continued high rates of new HIV infections and the life-prolonging impact of antiretroviral therapy (ART) [3].

Low bone mineral density (BMD) is common in HIV-positive patients. A meta-analysis of selected reports on bone loss in the whole HIV patient population (highly active antiretroviral therapy [HAART] treated plus naive) from 1994 to 2005 showed that these individuals had 6.4-fold increased odds of osteopenia and 3.7-fold increased odds of osteoporosis in comparison with uninfected individuals [4]. Opinions about the etiopathogenesis of osteopenia and osteoporosis during HIV infection are divergent. The patients infected with HIV are potentially at risk of osteoporosis because of traditional risk factors such as chronic illness, low body weight and body mass index (BMI), vitamin D deficiency, and the use of HAART. A meta-analysis showed that the prevalence of osteoporosis was 3 times higher among HIV-infected patients compared to HIV-negative controls [5]. The risk of fractures increases further in the aging HIV-infected population. Therefore, early detection and treatment of low BMD would be important preventive strategies for fractures in HIV-infected patients.

Thus, the present study is being undertaken to study the prevalence of low BMD in HIV-infected patients by dual-energy X-ray absorption (DEXA) scan and also to analyze the effect of various demographic determinants such as gender, BMI, CD4 count, and HAART on BMD of these patients.

MATERIALS AND METHODS

This observational cross-sectional study was conducted in Indira Gandhi Medical College, Shimla, which is a tertiary care center in North India over a period of 1 year, that is, from July 1, 2016, to June 30, 2017.

Inclusion and Exclusion Criteria

HIV-positive patients more than 18 years of age attending ART clinic or admitted in the medicine department (n=127) were included in the study after taking informed consent. Diagnosis of HIV was made as per the national guidelines for HIV testing based on enzyme-linked immunosorbent assay rapid and simple (E.R.S) and Western blot test using commercially available kits. Known osteoporotic subjects were included in the study for the prevalence data but not for the validation of risk score.

Subjects with comorbid conditions which could affect BMD such as neoplastic diseases, chronic renal disease, and liver disease were excluded from the study. Pregnant females, subjects with a history of fracture in the past 6 months or on artificial prostheses, and those who refused to give consent were also excluded from the study.

Ethical Considerations

Only those patients who consented to the study were included in the study. The whole information regarding the study was kept confidential and anonymity was maintained. The study involves minimal radiation exposure of 0.001 millisievert which is equivalent to 3 h of natural background radiation exposure and very less in comparison to maximum permissible exposure according to the International Commission on Radiological Protection for the general public, that is, 1 millisievert annually. Radiation hazard was explained to the patients before the study.

Methodology

After taking informed written consent, all eligible patients were subjected to a brief history, relevant physical examination, and a quick review of records. CD4 cell counts were measured by a fluorescent activated cell counter. Patients record of investigations including random blood sugar (RBS), hemogram, CD4 count, renal function tests, and liver function tests were reviewed.

BMD of the patients was determined using a whole-body densitometer, DEXA Scan (Dual Energy X-ray Absorption using HOLOGIC-Discovery QDR series 4500A DEXA machine). The patients were subjected to a DEXA scan at two sites: Lumbar spine and bilateral neck femur.

The measurements provided by DEXA were bone mineral content (in grams) and the projected area of the measured site (in square centimeters). Dividing bone mineral content by the area yielded BMD (in grams per square centimeter).

BMD was expressed in terms of standard deviation (SD) as a T score and a Z score. DEXA results were reported as numeric values for the T score and Z score and as a graphic curve normalized for gender and age. The Z score showed the difference between the patients BMD and the mean BMD of age- and gender-matched controls. A patient's BMD was given a T-score, which was derived by comparing it to an average score for a healthy 30 years old of the same sex and race. The difference between the "normal young" score and the patient's score was referred to as a SD. Those with BMD T-score between 0 and −1.0 were considered to be normal. Osteopenia was defined as a BMD T-score between −1.0 and −2.5, and osteoporosis was defined as a BMD T-score ≤ −2.5 using the WHO criteria [4].

Statistical Analysis

Data collected in the study tool were transferred into a Microsoft Excel sheet for further processing and analysis. The Statistical Package for the Social Sciences (SPSS) version 22 (American) and Epi Info version 7 software has been used for further analysis. A Chi-square test was applied on all the variables and $p>0.05$ was considered statistically significant.

RESULTS

A total of 127 HIV patients were evaluated. The mean age of patients was 40.3±8.107 years. Among these, 71 (55.9%) were male and 56 (44.1%) were female. We found that the mean weight was 55.86±10.526 (45–65 kg) and the mean height of 127 patients was 160.06±8.238 (152–168 cm). The mean BMI of 127 patients was 21.8047±3.83. (17.97–25.63) (Table 1).

We measured BMD at two sites: The lumbar spine and bilateral neck femur. The prevalence of low BMD (osteopenia/osteoporosis) was 82.67% (n=105). About 53 (41.7%) subjects had osteoporosis (Table 2). It was found that osteoporosis is maximum in the age group of >50 years and osteopenia in the age group of 41–50 years. The majority of subjects 20 (37.73%) were in the age group of 31–40 years (Table 3).

Table 1: The demographic characteristics of the participants (n=127)

Demographic characteristics	N	Mean
Age (years)		
Normal	22	37.41
Osteopenia	49	39.57
Osteoporosis	56	42.05
Total	127	40.29
CD4 count at admission		
Normal	22	283.36
Osteopenia	49	267.10
Osteoporosis	56	252.36
Total	127	263.42
CD4 count recent		
Normal	22	575.05
Osteopenia	49	479.20
Osteoporosis	56	441.98
Total	127	479.39
BMI (kg/m²)		
Normal	22	22.8873
Osteopenia	49	22.2259
Osteoporosis	56	21.0109
Total	127	21.8047

Table 2: Bone mineral density of subjects (n=127)

Dexa score	N	Mean	Std. deviation	Std. error	95% confidence interval for mean Lower bound	Higher bound	Minimum	Maximum
DEXA T score LS spine								
Normal	22	−0.486	0.3576	0.0762	−0.645	−0.328	−1.0	0.3
Osteopenia	49	−1.694	0.3960	0.0566	−1.808	−1.580	−2.4	−1.0
Osteoporosis	56	−3.118	.5721	0.0765	−3.271	−2.965	−4.9	−2.5
Total	127	−2.113	1.0968	0.0973	−2.305	−1.920	−4.9	0.3
Dexa BL femur T score								
Normal	22	−0.668	0.4314	0.0920	−0.859	−0.477	−1.5	−0.1
Osteopenia	49	−0.951	0.6914	0.0988	−1.150	−0.752	−2.8	0.2
Osteoporosis	56	−2.032	0.8233	0.1100	−2.253	−1.812	−4.0	−0.4
Total	127	−1.379	0.9263	0.0822	−1.541	−1.216	−4.0	0.2

DEXA: Dual-energy X-ray absorptiometry

Table 3: Correlation of age with bone mineral density

Age group in years	No. of patients	Normal	Osteopenia	Osteoporosis
18–30	15	3 (20)	6 (40)	6 (40)
31–40	54	12 (22.22)	22 (40.74)	20 (37.03)
41–50	44	7 (15.9)	19 (43.2)	18 (40.9)
>50	14	1 (7.14)	4 (28.58)	9 (64.28)

When BMD was correlated with gender, we found that males (88.73%) had low BMD than females (75%) (Table 4). Majority of the subjects having BMI <18 had low BMD (94.5%) and among subjects having BMI >18, 80.8% had low BMD. Hence, low BMD is more common in HIV-infected subjects with low BMI (Table 4).

For analysis, the CD4 count cutoff was taken at 400. In our study, 95 patients had baseline CD4 count <400 and 32 patients had CD4 count > 400. Seventy-nine out of 95 patients (83.15%) had low BMD and 26 out of 32 (81.2%) had low BMD. Thus, in our study, low BMD does not have a significant correlation with baseline CD4 count. After treatment, 47 patients had CD4 count <400 and 80 > 400. Forty-three out of 47 (91.5%) had low BMD and 62 out of 80 (77.5%) had low BMD. Thus, this study shows that patients having persistently low CD4 count even after treatment have higher chances of low BMD than those whose CD4 count had improved after treatment. Hence, CD4 count has a correlation to low BMD (Table 5).

A total of 126 subjects were on ART and one subject was on ART-naive. The most common regimen was tenofovir, lamivudine, and efavirenz (TLE) in 71 (55.9%) subjects followed by ZLN (zidovudine, lamivudine, and nevirapine) in 49 (38.58%) subjects. In patients on the TLE regimen, 33.8% had osteopenia and 50.7% had osteoporosis. The prevalence of low BMD was 84.5%. About 44.8% of patients on the ZLN regimen had osteopenia and 34.6% had osteoporosis and the prevalence of low BMD was 79.4% (Table 6).

DISCUSSION

In our study, the prevalence of low BMD (osteopenia/osteoporosis) was 82.67% (n=105) which is similar to the studies done by Sawlani *et al*. [6] (80%), Alonge *et al*. [7] (78.5%), and Paul *et al*. [8] (74%). The prevalence of osteopenia and osteoporosis was observed to be 38.6% and 44.1%, respectively, which is comparable with the studies done by Alonge *et al*. [7] and Sawlani *et al*. [6] where the prevalence of osteopenia and osteoporosis was reported to be 46.6% and 31.9% and 50.4% and 29.6%, respectively. The high prevalence of low BMD can be explained by the fact that the Indian HIV population lives in a resource-limited setting and a great proportion of them is diagnosed in an advanced stage of disease with frequent opportunistic infections [9]. Other factors such as malnutrition and Vitamin D deficiency may also be causing the increased prevalence of osteoporosis [8].

In our study, 53 (41.7%) subjects had osteoporosis and the majority of subjects 20 (37.73%) were in the age group of 31–40 years. Furthermore, BMD was found to be lower in males (61.2%) than in females (38.8%). Studies by Carr *et al*. [9] and Huang *et al*. [10] showed female predominance of lower BMD at each skeletal site. The results may be different from other studies because of less number of postmenopausal women in our study.

Low BMI is associated with low BMD. Studies conducted by Carr *et al*. [9], Paul *et al*. [8], and Loiseau-Peres *et al*. [11] found low BMD in low BMI. The result was not statistically significant (p=0.094) because of the small number of patients in the first group, that is, 18.

In our study, 95 patients had CD4 count <400 and 32 patients had CD4 count >400. The prevalence of low BMD in the first and second groups was 83.2% and 81.2% in DEXA lumbar spine but the result was not statistically significant (p=0.899). Thus, the baseline CD4 count of patients did not have a significant association with BMD in our study. We also observed the association of BMD with the present CD4 count of patients, that is, CD4 count at the time of the study. In our study, 47 patients had CD4 count < 400 and 80 patients had CD4 count >400. This shows that there is a definite improvement in CD4 count with antiretroviral treatment.

The prevalence of low BMD in the first and second groups was 91.5% and 77.5%, respectively, at the lumbar spine but the result was not statistically significant (p=0.61). Similarly, the prevalence of low BMD in both groups at bilateral neck femur was 72.4% and 57.6%, respectively, which was statistically

Table 4: Correlation of bone mineral density with gender and BMI

Gender/BMI	Normal	Osteopenia	Osteoporosis	Total	*P*-value
Gender					
Male					
Count	8	30	33	71	0.124
% within gender	11.3%	42.3%	46.5%	100.0%	
% within result	36.4%	61.2%	58.9%	55.9%	
Female					
Count	14	19	23	56	
% within gender	25.0%	33.9%	41.1%	100.0%	
% within result	63.6%	38.8%	41.1%	44.1%	
BMI (kg/m^2)					
<18					
18	1 (5.6%)	5 (27.7%)	12 (66.7%)		0.094
>18					
109	21 (19.2%)	44 (40.4%)	44 (40.4%)		

BMI: Body mass index

Table 5: Correlation of bone mineral density with CD4 count

CD4 count	No. of subjects (%)	Normal (%)	Osteopenia (%)	Osteoporosis (%)	*P*-value
At admission					
<400	95	16 (16.8)	36 (37.9)	43 (45.3)	0.899
>400	32	6 (18.8)	13 (40.6)	13 (40.6)	
At present					
<400	47	4 (8.5)	17 (36.2)	26 (55.3)	0.061
>400	80	18 (22.5)	32 (40.0)	30 (37.5)	

Table 6: Correlation of bone mineral density lumbar spine with ART regimen

Drug regimen	Normal (%)	Osteopenia (%)	Osteoporosis (%)
ZLN	10 (20.4)	22 (44.8)	17 (34.6)
TLE	11 (15.4)	24 (33.8)	36 (50.7)
ZLE		1 (100)	
SLN		1 (50)	1 (50)
ZL/atz/r		1 (100)	
ZL/lop/r			1 (100)
TL/atz/r	1 (100)		
Pre ART			1 (100)

TLE: Tenofovir, lamivudine, and efavirenz, ZLN: Zidovudine, lamivudine, and nevirapine, SLN: Slid lipid nanoparticles, AZT: Azidothymidine, ART: Antiretroviral therapy

significant with p=0.014, that is, low CD4 count is directly proportional to low BMD. This is in concordance with a study done by Sawlani *et al*. [6]

A correlation of BMD lumbar spine was done with ART regimen. Thus, low BMD was most commonly associated with the TLE regimen in our study. This can be explained on the basis of the use of tenofovir in the TLE regimen. Studies have shown that tenofovir has been strongly associated with an acute decrease in BMD. Two prospective studies conducted by McComsey *et al*. [12] and Stellbrink *et al*. [13] enrolled the subjects who were initiating their first ART regimen found that tenofovir-containing regimens led to a significantly larger decrease in the spine and hip BMD than ABC-containing regimens.

The mechanisms involved in bone loss associated with particular ART regimens are not well understood. TDF may affect bone indirectly through proximal tubule toxicity, resulting in phosphate wasting and increased bone turnover, whereas, EFV and PIs may affect BMD indirectly through Vitamin D metabolism.

A few limitations exist in our study. First, a comparison with HIV-negative controls was not made. Second, this study was done in a single center and the number of subjects studied was small. Furthermore, this was an observational study and not a prospective one, hence, it cannot establish a causal relationship of HIV with low BMD, and finally, other risk factors for low BMD such as Vitamin D levels, gonadal hormone levels, effect of alcohol, and tobacco use were not evaluated.

RECOMMENDATION

Recently, published guidelines for the management of low BMD in the general US population recommend a DEXA scan for persons of any age with a fragility fracture, women ≥65 years of age, and men ≥70 years of age [14]. For those with an additional risk factor, the recommendation is to perform a DEXA scan in younger postmenopausal women and men ≥50 years of age [14]. Although HIV infection is not listed as a condition

that is associated with low BMD, we believe that current evidence supports the inclusion of HIV infection among other risk factors. In our study, the mean age of osteoporosis is 46.5 years. Thus, we recommend a DEXA scan for all HIV-infected women and men >40 years.

CONCLUSION

Low BMD is prevalent in HIV-infected subjects. The causes of low BMD in individuals with HIV infection appear to be multifactorial. Low BMI, persistently low CD4 count, tenofovir-containing HAART regimen show a positive correlation with low BMD. HIV infection should be considered as a risk factor for bone disease. A DEXA scan should be done in all HIV-infected women and men >40 years and appropriate treatment should be started so as to prevent future fractures.

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