



Original Article

Prevalence and predictors of low bone mineral density in treatment-naïve HIV-infected patients and its correlation with CD4 cell counts

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ABSTRACT

Objective: HIV virtually affects every organ system of the body. The skeletal system is no exception, and antiretroviral therapy (ART) has been implicated in bone diseases. However, not many studies have been done to evaluate bone disease in treatment (ART) naïve HIV-infected patients, and hence, the present study was executed. **Materials and Methods:** One hundred and twenty HIV-infected ART-naïve patients and 80 age- and sex-matched healthy controls were recruited for this study. A thorough history and physical examination was done followed by laboratory investigations after an overnight fasting. Bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry scan at the level of lumbar spine, femur, and forearm. **Results:** Of 120 ART-naïve HIV-infected cases, the prevalence of osteoporosis and osteopenia was 13% and 41%, respectively, as compared to 0% and 17.5% in controls ($P < 0.001$). The mean BMD in cases was 0.842 g/cm² which was approximately 25% lesser than that in controls. Hypovitaminosis-D was seen in 100% of cases as compared to 65% of controls ($P < 0.01$). A significant association of low BMD was seen with HIV-infection *per se* ($P < 0.001$), low CD4 cell counts ($P < 0.001$), low Vitamin D levels ($P < 0.001$), long duration of disease ($P < 0.04$), history of opportunistic infections ($P < 0.03$), and history of tuberculosis in the past ($P < 0.05$). **Conclusion:** Bone diseases such as osteoporosis and osteopenia characterized by low BMD are very common in HIV-infected patients. Virus *per se*, along with low CD4 cell counts and low Vitamin D levels are major predictors of pathological fractures in these individuals.

KEYWORDS: Bone mineral density, CD4 counts, HIV/acquired immunodeficiency syndrome, Osteopenia, Osteoporosis

Submission : 08-Aug-2019
Revision : 23-Aug-2019
Acceptance : 02-Sep-2019
Web Publication : 10-Apr-2020

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS), since its first detection in the USA in 1981 has evolved from a mysterious illness to a global pandemic. The number of patients infected with human immunodeficiency virus is increasing tremendously and alarmingly. HIV infection has myriad effects on endocrine and metabolic machinery of the body, including the skeletal system [1]. The medications used for therapy also affect bone metabolism and contribute to bone loss. The resulting vulnerable bone predisposes the individual to increased risk of debilitating fractures, thereby compromising the quality of life [2]. Much research has been done regarding the effect of highly active antiretroviral treatment therapy (HAART/ART) and opportunistic infections (OIs) on bone mineral density (BMD), but the effect of HIV *per se* on BMD has not been studied well so far in this part of the world. The present study focuses on the estimation of BMD

in patients infected with HIV but not on ART, i.e. ART-naïve cases, and to find the predictors of abnormal BMD and risk of pathological fracture in these individuals.

MATERIALS AND METHODS

It was a cross-sectional observational study done at a tertiary care center in New Delhi, India, over a span of 1 year. The study was approved by institutional review board and ethical committee (Number: 23-1/2012/Acad./PGIMER). The cases included 120 ART-naïve HIV-infected patients. Eighty HIV non-infected age- and sex-matched healthy volunteers


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How to cite this article: Gupta PK, Singh S, Mahto SK, Sheoran A, Garga UC, Lal AK, et al. Prevalence and predictors of low bone mineral density in treatment-naïve HIV-infected patients and its correlation with CD4 cell counts. Tzu Chi Med J 2021; 33(1): 49-54

Access this article online	
Quick Response Code: 	Website: www.tcmjmed.com
	DOI: 10.4103/tcmj.tcmj_177_19

were included as controls. Bilingual consent was taken from cases and controls. The permission from institutional ethics committee was obtained.

All individuals taking calcium supplements, bisphosphonates, antiepileptics, multivitamins (including Vitamin D preparations), steroids or individuals with a history of present or past fracture at the sites used for dual-energy X-ray absorptiometry (DEXA) scan were excluded. Patients with a history of chronic kidney or liver disease, diabetes mellitus, hypertension, hypothyroidism, parathyroid-related disorders, malignancy, cases with active or chronic alcoholism, and smoking were excluded. All cases with any history of OI's (at the time of study or within the past 6 months) were also excluded. All cases underwent baseline investigations for HIV-infected patients as per the National AIDS Control Organization (NACO) guidelines including complete hemogram, liver and kidney function tests, CD4 cell counts, HBsAg, anti-HCV, and VDRL testing. BECTON-DICKINSON FACS flow cytometer was used to obtain CD4 cell counts. 25-hydroxy (25-OH) Vitamin D levels were measured by ELISA technique using Bio Rad Evolis Twin plus automatic workstation. Vitamin D deficiency was defined as fasting serum 25(OH) D levels below 20 ng/ml, and Vitamin D insufficiency was defined as fasting serum 25(OH) levels of 21–29 ng/mL, levels >30 ng/mL were taken as normal [3].

All the cases and controls were subjected to three sites DEXA scan at lumbar spine, bilateral femur, and forearm to measure BMD. BMD was expressed in absolute terms of grams of mineral per square centimeter (g/cm^2) and as a relationship to two norms: compared to the expected BMD for the patient's age and sex (Z-score), or compared to "young normal" adults of the same sex (T-score). The difference between the patient's score and the norm was expressed in standard deviations (SD) above or below the mean (1 SD being equal to 10 to 15% of the BMD value in g/cm^2). The DEXA Machine used was Discovery Wi (S/N 84571) manufactured by HOLOGIC. The BMD diagnosis of normal, low bone mass (osteopenia), osteoporosis, and severe or established osteoporosis was based on the WHO diagnostic classification [2].

Normal

BMD is within 1 SD of a "young normal" adult (T-score at -1.0 and above).

Osteopenia

BMD is between 1.0 and 2.5 SD below that of a "young normal" adult (T-score between -1.0 and -2.5).

Osteoporosis

BMD is 2.5 SD or more below that of a "young normal" adult (T-score below -2.5). Patients in this group who have already experienced one or more fractures were deemed to have severe or "established" osteoporosis.

Statistical analysis

The analysis was carried out in Microsoft Excel 2007 and SPSS software (IBM Corp. Statistical for Windows, Version 20.0 Released 2011 Armonk, NY, USA). The *t*-test was used to determine the difference in the means of two groups. The quantitative variables were reported as mean \pm SD

and Pearson's test was used to calculate the correlation. The level of $P \leq 0.05$ was considered of statistical significance.

RESULTS

A total of 120 HIV-infected cases not on ART were enrolled in this study with a control group of 80 age- and sex-matched HIV-negative healthy volunteers. The cases included 98 males and 22 females, and the control group included 60 males and 20 females. All cases and controls were in the age group of 18–40 years with a mean age of 31.70 years for HIV-positive cases and a mean age of 29.96 years for the controls. The baseline characteristics were largely comparable in the two groups [Table 1]. The mean duration of disease (from the day of diagnosis of HIV infection) among cases was 2.4 years (range 1–6 years). The mean CD4 cell counts in the cases were 315.68 cells/ mm^3 . The cases were further divided into three groups according to the level of immunosuppression and the CD4 cell counts [Table 2].

The mean BMD among cases was 0.842 g/cm^2 as compared to 1.112 g/cm^2 in controls ($P < 0.001$) (95% confidence interval [CI] 2.32–4.48), i.e. the mean BMD among patients infected with HIV was about 25% less than the BMD of normal healthy population. The prevalence of osteoporosis and osteopenia among cases was 13% and 41%, respectively, as compared to 0% and 17.5% in controls ($P < 0.001$) (95% CI 2.12–3.32) implying that less than half of the cases had normal BMD whereas almost 83% of controls had normal BMD. The cases in Group A had significantly lower BMD as compared to Group B ($P < 0.01$, CI 1.23–1.77) and Group C ($P < 0.001$, CI 2.11–4.3), respectively [Table 3]. Similarly, the mean Vitamin D levels among cases was 16.083 \pm 3.23 ng/mL (range 4.280–26.45 ng/mL) and the same in controls was 24.74 \pm 4.212 ng/mL ($P < 0.01$) (95% CI 1.16–1.74). About 71% of cases as compared to 9% of controls had severe Vitamin D deficiency ($P < 0.001$) (95% CI 2.61–3.91) whereas 29% of cases had insufficient Vitamin D as compared to 56%

Table 1: Correlation of lab and anthropometric parameters with bone mineral density in cases and controls

Parameter	Mean value (cases)	Mean value (controls)	P
Age (years)	31.70 \pm 7.42	29.96 \pm 5.70	0.34
Hemoglobin (g/dL)	13.45 \pm 2.83	14.18 \pm 2.03	0.09
Serum protein (mg/mL)	6.93 \pm 1.12	7.12 \pm 1.23	0.21
BMI (kg/m^2)	24.48 \pm 4.26	25.12 \pm 3.07	0.12
WHR	0.89 \pm 0.06	0.87 \pm 0.09	0.10
Serum cholesterol	182 \pm 31.17	176 \pm 24.12	0.27

WHR: Waist-hip ratio, BMI: Body mass index

Table 2: Division of cases according to the level of immunosuppression

CD4 counts	HIV-associated immunodeficiency	Group	Number of patients	Mean CD4/ μL
<350/ mm^3	Severe	A	65	224 \pm 40.88
350–500/ mm^3	Advanced	B	29	387 \pm 45.53
\geq 500/ mm^3	Mild	C	26	512 \pm 57.77
Total			120	315.68 \pm 46.88

HIV: Human immunodeficiency virus

of controls. All of the cases (100% had hypovitaminosis-D compared to 65% of the controls. ($P < 0.01$) (95% CI 1.46–2.42). Among all cases, 83% in Group A as compared to 42% in Group C had Vitamin D deficiency, and the correlation of levels of Vitamin D with CD4 cell counts was statistically significant ($P < 0.001$) (CI 2.20–3.35) [Figure 1].

At the level of lumbar spine the BMD was measured at L1, L2, L3, and L4 vertebrae. The mean BMD among cases was 0.814 g/cm² (range 0.678–0.835 g/cm²) as compared to 1.198 g/cm² in controls ($P < 0.001$) (95% CI 1.71–2.46). The mean T score at lumbar spine was -1.295 ± 0.42 as compared to -0.898 in controls ($P < 0.001$) (95% CI 1.34–1.96). Majority of the cases (50%) had osteopenia whereas 21 cases (17.5%) had osteoporosis. Thus, at the level of lumbar spine only 32.5% of the cases as against 85% of controls had normal BMD where as 12 (15%) had osteopenia and none had osteoporosis. Among cases in Group A, i.e. patients with severe immunodeficiency, 41 cases (66%) had osteopenia and 21 cases (32%) had osteoporosis, and only three cases had normal BMD. No case in Group B and Group C had osteoporosis and 19 cases in Group B and only 1 in Group C had osteopenia. Among all the cases, a strong association was found between low CD4 cell counts and reduced BMD at lumbar spine ($P < 0.001$) (95% CI 1.61–2.42). Similarly, low Vitamin D levels also showed a strong association with low BMD at lumbar spine ($P < 0.001$) (95% CI 2.22–3.61). No significant association was found between BMD and age of the cases or the duration of disease. However, cases with a history of any OI had significantly more chances of having low BMD ($P < 0.03$) as compared to those who never had these OIs.

At the level of femur (femoral neck and greater trochanter) the mean BMD among cases was 0.851 g/cm² (range 0.748–0.93 g/cm²) as compared to 1.142 g/cm² in controls

($P < 0.001$). The mean T score among cases and controls was -1.273 ± 0.24 and -0.97 ± 0.11 ($P < 0.001$), respectively. At the level of femur, 51 (43%) cases had osteopenia and 14 (12%) had osteoporosis and only 55 cases (45%) had normal BMD. Among controls, none had osteoporosis and 12% had osteopenia. A strong statistical association was found between low BMD and low CD4 cell counts ($P < 0.001$, 95% CI 2.06–4.66), as well as low Vitamin D levels ($P < 0.01$, 95% CI 1.19–2.14). Unlike at lumbar vertebra, at the level of femur the duration of disease was also seen to be significantly associated with low BMD ($P < 0.04$, 95% CI 1.01–1.13) However, no statistical association was seen with history of OIs.

At the level of forearm, 30 (25%) cases had osteopenia, and 11 (9.5%) had osteoporosis while 79 (66%) cases had normal BMD. In the control group, only 10 (12%) showed the presence of osteopenia, and none had osteoporosis. The mean T score in the cases was -0.97 ± 0.17 compared to -0.78 ± 0.12 in controls ($P < 0.01$). The mean BMD among cases at forearm was 0.902 g/cm² as compared to 1.125 g/cm² in controls ($P < 0.01$) (95% CI 1.60–2.12). A statistically significant association was seen between low CD4 cell counts and low BMD ($P < 0.01$) (CI 1.3–1.9). No statistically significant association was obtained between BMD at the level of forearm with age, duration of the disease, history of OIs, or Vitamin-D levels.

Taking all the sites into account, the overall prevalence of osteoporosis and osteopenia among cases was 24% and 54%, respectively, and normal BMD at all three sites was seen in only 21% of cases infected with HIV/AIDS [Table 4 and Figure 2].

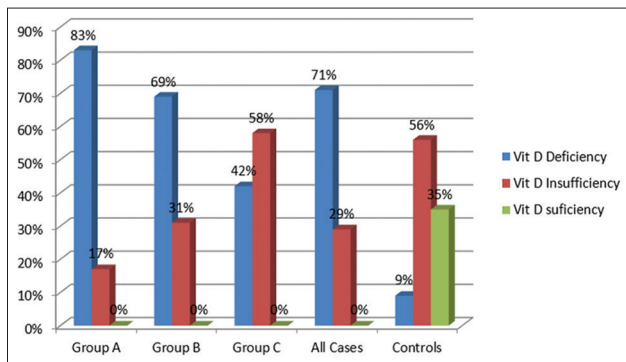


Figure 1: Bar diagram depicting the prevalence of hypovitaminosis-D in HIV-infected cases and controls

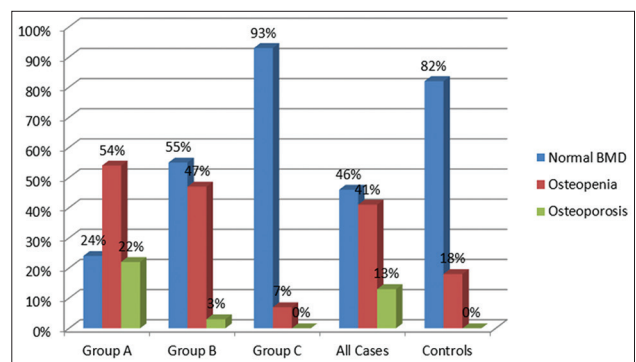


Figure 2: Bar diagram depicting the prevalence of low bone mineral density in HIV-infected cases and controls

Table 3: Vitamin D levels and bone mineral density in cases according to the severity of immunosuppression

CD4 groups	Vitamin D3 levels (%)			BMD (%)		
	<20 ng/mL (deficient)	>21–29 ng/mL (insufficient)	>30 ng/mL (sufficient)	Normal	Osteopenia	Osteoporosis
A	54 (83)	11 (17)	0	16 (24)	35 (54)	14 (22)
B	20 (69)	9 (31)	0	16 (55)	12 (47)	1 (3)
C	11 (42)	15 (58)	0	24 (93)	2 (7)	0
Total (120)	85 (71)	35 (29)	0	56 (46)	49 (41)	15 (13)
Controls (80)	7 (9)	45 (56)	28 (35)	66 (82)	14 (18)	0

BMD: Bone mineral density

Table 4: Bone densitometry at different sites among different group of cases and controls

CD4 groups	Spine (%)			Femur (%)			Forearm (%)		
	Normal	Osteopenia	Osteoporosis	Normal	Osteopenia	Osteoporosis	Normal	Osteopenia	Osteoporosis
A (65)	3 (5)	41 (63)	21 (32)	13 (20)	38 (58)	14 (22)	36 (55)	22 (34)	7 (11)
B (29)	10 (34)	19 (66)	0	19 (66)	10 (34)	0	21 (73)	7 (24)	1 (3)
C (26)	25 (96)	1 (4)	0	23 (88)	3 (12)	0	22 (85)	1 (3)	3 (12)
Total (120)	38 (32)	61 (50)	21 (18)	55 (46)	51 (42)	14 (12)	79 (66)	30 (25)	11 (9)
Controls (80)	68 (85)	12 (15)	0	70 (87)	10 (13)	0	76 (95)	4 (5)	0

DISCUSSION

Bone demineralization is a complex phenomenon influenced by multiple factors including age, sex, biochemical parameters, Vitamin D levels, BMI, as well as obesity and physical activity. About 20% of the normal healthy population can have osteopenia and up to 10% can have osteoporosis [4]. However, the prevalence of osteopenia and osteoporosis varies with age and is seen to be 25% and 6%, respectively, in 40–50 years of age group and 28% and 32% in 70–80 years of age group, respectively [4]. Overall, the prevalence of osteopenia and osteoporosis in general healthy population in Delhi is considered to be 24% and 6.9%, respectively (females > males) and is much less in young individuals <40 years of age [5].

The reported prevalence of osteoporosis in women was 15% in France and Germany, 9% in the United Kingdom, and 38% in Japan, 16% in the USA, whereas in men the prevalence was 3% in Canada, 1% in the United Kingdom, 8% in France, and 4% in Japan [6]. The prevalence of osteoporosis in Caucasian women aged more than 50 years ranges from 7.9% to 22.6% [7]. The prevalence of osteoporosis in the forearm in the Nutrition and Health Survey in Taiwan was found to be 25.0% in women and 11.6% in men [8]. All the data suggested that osteoporosis is a common disease worldwide; however, compared with other countries not much is known about the epidemiological characteristics of osteoporosis in India. Kaushal *et al.* [5] in a retrospective study on 524 individuals in Delhi revealed that rate of the osteoporosis in males of the age group 30–39, 40–49, 50–59, 60–69, and ≥70 years were 0%, 4%, 6.5%, 4.3%, and 5.6%, respectively, and in females, the rate was 3%, 3.4%, 14.3%, 18.6%, and 36.4%, respectively, in the age groups at the level of lumbar spine.

In our study, 41% of cases had osteopenia as compared to 17.5% in the healthy controls. Osteoporosis was seen in 13% of cases and none of the controls. The difference was statistically significant implying that the infection with HIV itself is a predictor of low BMD in these groups of individuals. This can be explained by the fact that HIV can infect bone marrow structural cells in early stages, and HIV infection of preosteoblastic marrow structural cells can adversely affect their differentiation into osteoblasts. This, however, does not coincide with the results of Bolland *et al.* [9] who concluded that HIV-infected ART-naive men and even those treated with ART have similar BMD as healthy controls. According to Ofotokun *et al.* [10] HIV infection may have both direct and indirect effects on osteoclasts. The pathogenesis of excess bone loss associated with HIV is complex and multifactorial. Bone loss may result from pathophysiologic interactions within the bone microenvironment between

T cells, osteoclasts and osteoblasts, promoted by elements of both HIV infection and its therapy. In addition, bone loss may result from nutritional and hormonal changes commonly associated with HIV infection, such as wasting, malnutrition, malabsorption, and calcium and Vitamin D deficiency. The demographic and cultural factors such as restricted social and outdoor movements of HIV patients also play an important role. In a developing country like India, HIV/AIDS is considered a major social stigma and patients restrict themselves indoors and hence have limited mobility leading to bone demineralization. Malnutrition is also very common, with predominantly high carbohydrate diet and low calcium and protein intake. HIV/AIDS is a disease of low-income group in India, and other factors such as loss of employment and depression may contribute to osteoporosis, the prevalence of which was found to be even higher than that reported in patients with rheumatoid arthritis (15%) [11] or diabetes mellitus (15%) [12]. We found a significant association of low BMD with longer duration of disease. This can be explained by the fact that during this whole duration of infection with HIV, i.e., average 2.4 years, the cases were ART-naive with probably higher viral load and hence more virus and cytokine associated bone catabolism and related bone injury.

Another significant contributor to low BMD in our cases was hypovitaminosis-D which was seen in 100% of cases. Vitamin D is necessary for calcium absorption from intestines. Calcium makes bone dense and strong, and low Vitamin D can cause soft, thin, brittle bones manifesting as osteoporosis in adults and rickets in children. Vescini *et al.* [13] concluded that 54% of their HIV-infected study population had Vitamin D insufficiency and 7% had Vitamin D deficiency. Similarly, Kim *et al.* [14] concluded that 21% of HIV-infected patients have Vitamin D deficiency and 50% have insufficiency. Studies in India have reported that 60% of the general population may have hypovitaminosis-D. A probable explanation to this increased hypovitaminosis-D in HIV-infected population is that the virus *per se* as well as accompanying OIs especially gastrointestinal lead to malnutrition or underlying subclinical low-grade inflammation in various tissues in patients with HIV/AIDS. The virus produces pro-inflammatory cytokines such as TNF-alpha and interferon-gamma which can interfere with the enzymes of Vitamin D synthesis pathway. Interferon-gamma induces the enzyme 1-alpha-hydroxylase in macrophages directly or indirectly via toll-like receptors (TLRs) which leads to a decrease in levels of 25-OH Vitamin D [15]. Apart from this, HIV-infected patients share common risk factors for Vitamin D deficiency found in the general population, i.e., aging, low

sunlight exposure, dark-colored skin, low consumption of fortified foods or malnutrition [16].

Fessel *et al.* [17] found that the prevalence of osteopenia and osteoporosis in HIV-infected patients was 18% and 3.8%, respectively. This figure is much lower than 41% and 13% obtained in our study. One of the reasons behind this is that our study had a significant number of patients with low CD4 cell counts and hence possibly underlying viremia was high leading to presumably more osteoclastic activity and hence lower BMD, with higher incidence of osteopenia and osteoporosis. Apart from that, our patients were ART-naïve and thus likely to have higher viral load. Since routinely, ART is being started on the day of diagnosis internationally, so very little western data are available regarding BMD in ART-naïve patients. Grant *et al.* [18] concluded that low pretreatment CD4 cell counts are a strong and independent risk factor for bone loss after ART initiation. He also stated that ART initiation at higher CD4 cell counts may reduce the burden of osteoporosis and fragility fractures. Although, they could not find any correlation of low CD4 cell count with BMD in treatment-naïve patients. However, the mean CD4 counts in their study were significantly higher than ours, and very few had low Vitamin-D levels. Yong *et al.* [19] in Australia concluded that HIV-infected individuals with low CD4 counts have lesser BMD and 88% of these patients with low impact trauma fracture have either osteoporosis (56%) or osteopenia (32%).

In our study, the CD4 cell counts obtained in patients having osteoporosis and osteopenia were considerably lower, signifying a statistically significant association between low CD4 cell counts and reduced BMD. This may be explained by the late presentation of patients to centres providing treatment for HIV/AIDS and ART clinics in India, and the fact that till early 2017, ART in India was started late (at CD4 cells counts $<350/\mu\text{L}$), so physicians used to wait till CD4 values dropped to this levels causing a prolonged as well as more severe virus-related bone injury. Secondly with such low CD4 cell counts, patients frequently used to acquire subtle OIs which by themselves can cause demineralization and may also result in malnutrition, more catabolism, limitation in mobility, and hence low BMD.

In our study, the only factors affecting BMD in cases were low CD4 cell counts, long duration of disease, history of OIs, and low Vitamin D levels. On the contrary Brown *et al.* [20] found a much lesser prevalence of low BMD (10%) in HIV-infected patients and concluded that among ART-naïve HIV-infected patients, low BMD was associated with lower lean mass, higher adiponectin, and lower osteoprotegerin but not HIV-related disease variables or any of the metabolic inflammation markers. The reason behind this difference is that their cases had reasonably good CD4 cell counts ($>500/\mu\text{L}$). Apart from that, the duration of disease was shorter (<1 year). Bonjoch *et al.* [21] in their study on HIV-infected people on HAART found osteopenia and osteoporosis in 47.5% and 23%, respectively, and found that the factors associated with bone loss and progression were age, male sex, low body mass index, time on protease inhibitor, time on tenofovir therapy, and current use of protease inhibitors. However, the mean CD4 counts of their cases were much lower as compared to

ours, and most patients were on protease inhibitors, which by itself are known to reduce BMD significantly as compared to our cases which were drug-naïve.

In present times, with the current management and early initiation of ART, mortality with HIV infection is decreasing and so the patients are living longer; therefore, the focus has now shifted to comorbid complications and measures to ameliorate the same. Hence, we conclude that measures should be taken in HIV patients especially with low CD4 cell counts to maintain bone health. Since low BMD predisposes these patients to pathological fractures, especially in the axial skeleton, hence supplementation with Vitamin D and bisphosphonate should be considered in these cases. The study has highlighted the growing problem of reduced bone density in patients of HIV and would help in planning appropriate palliative therapy required in such patients and consequently improving their functional status.

Limitations of the study

The cross-sectional nature of this study does not allow us to conclude the cause effect relationship of HIV virus or low CD4 cell counts with low BMD. Viral load levels would have been desirable to prove the role of human immune deficiency virus *per se* in causation of osteoporosis. A FRAX score along with serum parathyroid hormone levels and sex hormone levels would have added weight to the results.

CONCLUSION

Infection with HIV *per se*, and low CD4 cell counts was found to be significantly associated with low BMD and low T score at lumbar spine, femur, and forearm. Similarly, low Vitamin D3 levels were found to be associated with low BMD at the spine and femur but not at the forearm. The long duration of disease and history of OIs were seen to be associated with low BMD at femur ($P < 0.04$) and spine ($P < 0.03$), respectively. History of tuberculosis anytime in the past was also seen to be associated with low BMD ($P < 0.05$). No statistically significant association was found between BMD and age or sex of the patient, body mass index, waist-hip ratio, or any other biochemical parameter including serum proteins, lipids, and hemoglobin. BMD among cases infected with HIV/AIDS was very low at femur and spine but a little better at forearm making these individuals vulnerable to pathological fractures at the above-mentioned sites.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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