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Evaluation of bone mineral density and its influencing factors in patients infected with HIV under antiretroviral therapy

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Abstract

Background Reduced Bone Mineral Density (BMD) has been linked to Human Immunodeficiency Virus (HIV) infection and treatment. There is a lack of information regarding the osteoporosis status of middle-aged patients with HIV in Iran, despite the fact that Antiretroviral Therapy (ART) is widely accessible.

Objective The purpose of this cross-sectional study was to assess the BMD status and low BMD risk factors in patients with HIV under ART living in Iran.

Methods Data were collected from individuals diagnosed with HIV aged 30–50, receiving ART for at least 6 months. Dual-energy X-ray absorptiometry scans assessed BMD in femoral neck, total hip, and lumbar regions. Pearson's correlation coefficients identified relationships between BMD and demographic and laboratory predictors. Univariable and multivariable logistic regression models assessed predictors of low lumbar BMD.

Results Among 80 HIV-infected individuals (mean age: 41.1 ± 5.6 years, 60.4% male), 15% exhibited low BMD in the lumbar spine and 3.75% in the femoral neck. Serum phosphate levels were negatively correlated with BMD across the femoral neck, total hip, and lumbar regions (e.g., lumbar BMD: r = -0.24, p = 0.03). Parathyroid hormone (PTH) showed negative correlations with femoral neck and total hip BMD (r = -0.26, p = 0.01; r = -0.29, p = 0.01, respectively). Estradiol positively correlated with lumbar BMD in females (r = 0.36, p = 0.04), and BMI positively correlated with BMD in all regions (e.g., lumbar: r = 0.41, p = 0.001). Testosterone was inversely associated with the odds of lumbar low BMD (OR [95% CI] = 0.79 [0.62–0.96], p = 0.02). Duration of HIV or treatment, CD4 levels, and viral load were not significantly associated with BMD.

Conclusion This study highlights the multifactorial nature of BMD changes in individuals living with HIV. By identifying correlations between metabolic, hormonal, and disease-related factors and bone health, our findings

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bring attention to an often-overlooked aspect of HIV management, that is patients with HIV may benefit from routine BMD screening, as it could help identify early risks of low BMD.

Keywords HIV, Bone mineral density, Antiretroviral therapy, Osteoporosis, Risk factors

Introduction

Human Immunodeficiency Virus (HIV) is a major health issue, having claimed millions of lives with considerable burden contributions from many countries across the world [1]. Based on 2022 data, approximately 39.0 million [33.1–45.7 million] people are living with HIV globally, with 3.9 million [3.4–4.6 million] in Southeast Asia, 25.6 million [21.6–30.0 million] in Africa, 3.0 million [2.6–3.3 million] in Europe, and 3.8 million [3.4–4.3 million] in the American region [2]. Thus far, the precise incidence of HIV in the Middle East region, in which Iran is located, is not available. HIV has a major negative impact on patients, potentially causing Acquired Immunodeficiency Syndrome (AIDS) by increasing morbidity and mortality [3], and its following complications, of note, bone loss [4], so much so that every ten years of life beyond thirty, the risk of osteoporosis rises by 1.4 to 1.8 times [5–7]. Common global risk factors for HIV-associated reduced bone mineral density include low body weight [8], age more than 50 [8], lower CD4 count [9], diabetes [9], low calcium and vitamin D diets, physical inactivity, smoking [10], and direct effects of the virus on BMD [11, 12].

HIV as well as antiretroviral treatment are important factors giving rise to secondary osteoporosis, especially thanks to widespread access to Antiretroviral Treatment (ART) [11]. The antiviral effects of Highly Active Antiretroviral Therapy (HAART), which combines two or three medications that target several stages of the HIV life cycle, are synergistic. Long-term use, however, may result in metabolic issues such as mitochondrial malfunction, oxidative stress, and inflammation [13]. The number of people living with HIV has increased due to treatment with antiretroviral medication, with a cumulative decrease in the AIDS-related mortality rate [14]. The impact of age on HIV treatment is significant and may further result in senile osteoporosis [15, 16]. HIV virus proteins enhance osteoclast activity and osteoblast apoptosis, limiting bone production, whereas viral infection can alter BMD through systemic inflammation and bone remodeling [17]. Studies corroborate the claims, reporting a greater incidence of osteoporosis among people with HIV [18]. Compared to other infected patients, HAART-treated patients infected with HIV had an almost threefold higher prevalence of osteoporosis [11]. Treatment type has a substantial impact on bone loss, and nucleotide reverse transcriptase inhibitors are linked to a drop in BMD [19–21].

As per the findings of the Iranian national HIV registry system report, 38,966 individuals received an HIV positive diagnosis by the close of 2018. It further underscores the paramount importance of our study that the mean age of the patients is on the rise, with the majority aging between 31 and 50 [22]. Given the lack of data regarding the status of osteoporosis in middle-aged patients with HIV in Iran, this cross-sectional study aims to investigate the BMD in Iranian patients with HIV in order to further ascertain the regional risk factors impacting bone density [23, 24].

Methods

Study design and participants

This investigation is a cross-sectional study. Sample size was calculated using a prior analysis with parameters including a one-tailed large sample z-test and a lumbar BMD odds ratio of 1.91 according to previous Iranian populations with HIV [25–28], aiming for an alpha error probability of 0.05 and a statistical power of 0.80, resulting in a total sample size of 96 participants. The population was collected using convenient sampling from 3,000 patients of the HIV Clinic of Imam Khomeini Hospital data registry due to the hard-to-reach nature of patients with HIV. In this study, we excluded patients suffering from any endocrine disease such as diabetes mellitus, hyperthyroidism, Cushing's syndrome, hyperparathyroidism, malabsorption, drugs with known effects on bone health status, infections, malignancy, and autoimmune diseases. Additionally, patients who were pregnant or already undergoing treatment for osteoporosis were excluded from the study. We gathered data from 96 men and women between the ages of 30 and 50 diagnosed with HIV who received a fixed treatment regimen for at least 6 months and were referred to the HIV Clinic of Imam Khomeini Hospital between 2021 and 2023. Eighty patients consented to undergo a Dual-energy X-ray Absorptiometry scan (DXA).

Study measurement

Volunteers were selected from patients referred to the HIV Clinic of Imam Khomeini Hospital for treatment. The collected data included general demographic characteristics, including gender, smoking and alcohol consumption, age, and Body Mass Index (BMI) (height and weight measurement was performed by a trained nurse); HIV-associated factors, including viral load, HIV treatment regimen, HIV disease duration, CD4+T-cell count, and HIV treatment duration; routine laboratory tests,

including Creatinine (Cr), Calcium (Ca), Phosphate (P), Alkaline Phosphatase (Alkph), 25-hydroxyvitamin D (25(OH)D), Fasting Blood Sugar (FBS) using the Cobas c311 analyzer (Roche, Mannheim, Germany); and hormonal assays, including Parathyroid Hormone (PTH), Thyroid-Stimulating Hormone (TSH), Free Thyroxine (Ft4), testosterone, estradiol, Luteinizing Hormone (LH) using the Cobas e411 analyzer (Roche, Mannheim, Germany); CD4 counts were measured by flow cytometry. Sampling was done in fasting conditions according to standard protocols. Then, the referral form was delivered to the individuals, and the volunteers were referred to the bone density measurement department of the hospital of the contracting party of the project (Diabetes Clinic). If the person under study had used radioactive substances or drugs containing calcium in the last 5 days, the bone density test was postponed for at least 5 days after that.

Bone mineral density assessment

BMD was assessed using the DXA device Hologic Discovery Model A. Bone mineral density was measured using the local DXA method in three locations of the total femur, lumbar vertebrae, and femoral neck, along with a full body scan with DXA. The DXA device was regularly reviewed by the daily standard and a special phantom for control and measurement. Density values were obtained based on grams per square centimeter. Since the age of our patients ranged from 30 to 50 years, the use of Z-scores (defined as an individual's BMD in comparison to age-matched normal individuals) was used for all the analyses, according to the World Health Organization's (WHO) recommendation [29].

Variable definition

We considered a serum 25(OH)D concentration of 30 ng/mL as a threshold value for identifying low levels of vitamin D, as previously reported (standard value of our laboratory: 30–80 ng/mL) [30]. Participants were categorized as having low BMD if the femoral neck or lumbar spine Z-score was −2 or less. Osteoporosis and osteopenia were defined as a T-score ≤ -2.5 standard deviation (SD) and between −1 and −2.5 SD below the young adult mean value, respectively [31]. The decision to report both T-scores and Z-scores was made to address different aspects of the data and the statistical assumptions underlying each test.

Statistical analysis

After collecting the data, they were entered into SPSS 26 (SPSS, Inc., Chicago, IL) software. After performing normality tests and ensuring the normality of the research data distribution, numerical variables were reported as mean±SD or median and interquartile range (IQR) and categorical variables were reported as number and percentage. All tests with a p-value<0.05 were considered significant.

Linear correlation analysis was performed, and the test on Pearson's linear correlation coefficient r was performed with the t-Student test under the null hypothesis of Pearson's linear correlation coefficient r=0. A heatmap was drawn to demonstrate the correlation coefficients between our variables and BMDs, ranging from dark blue (least correlation) to red (most correlation). Statistically significant correlation coefficients are marked.

The univariable logistic regression was performed to analyze the relationship between low BMD of the lumbar region (dichotomous variable) as the dependent outcome and the independent variables, such as gender (dichotomous), smoking and alcohol (dichotomous), BMI (continuous), CD4 cells (continuous), and 25(OH)D (continuous). Multivariable logistic regression was performed using the enter method. This approach includes all variables with a P-value of <0.2 from the univariable models.

Ethical consideration

The study protocol was reviewed and confirmed by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1400.139). Written informed consent was obtained from all participants.

Results

The total number of participants in the study was 96, and due to the refusal of 16 patients for DXA and the requisite tests, the final number was reduced to 80. Of 80 included patients according to lumbar T-score, 12 fell into the category of low BMD and the other 68 were normal BMD. The majority of the participants were male (60.4%). The mean age of the study population was 41.1 years (±5.6 SD). Table 1 comprehensively summarizes the population baseline characteristics.

Regarding the prevalence of different BMDs as assessed by T scores, in the femoral neck region, 1.3% of patients fall into the category below −2.5, 40% fall between −2.5 and −1, and 58.7% have T scores above −1. In the total hip region, none of the patients fall below −2.5, 15% fall between −2.5 and −1, and 85% have T scores above −1. In the lumbar region, 5% of patients fall below −2.5, 38.8% fall between −2.5 and −1, and 56.2% have T scores above −1. However, based on the Z score, in the femoral neck region, 96.25% of cases had a Z score greater than or equal to -2, while 3.75% had Z scores less than −2. In the total hip region, all cases (100%) had a Z score greater than or equal to -2. In the lumbar region, 85% of cases had a Z score greater than or equal to -2, while 15% had Z scores less than −2.

Several factors showed correlations with BMD, including serum phosphate levels, which showed a significant negative correlation with femoral neck BMD (r = -0.31,

Table 1 Main characteristics of patients

Categorical variables		**Groups**	
Variables	**Total population (*n* = 80)**	**Low lumbar BMD group (*n* = 12)**	**Normal lumbar BMD group (*n* = 68)**
Male	58 (72.5)	10 (83.3)	38 (55.9)
Smoking	33 (41.3)	4 (33.3)	22 (32.4)
Alcohol	14 (17.5)	2 (16.7)	8 (11.8)
Detectable viral load	13 (16.3)	11 (91.7)	57 (83.6)
Treatment regimen			
Truvada + Dultegravir	39 (48.8)	5 (41.7)	34 (50.8)
Vonavir	24 (30.0)	4 (33.3)	20 (29.9)
Truvada + Atazanavir	4 (5.0)	2 (16.7)	2 (3.0)
Tenofovir + Efavirance	3 (3.8)	-	3 (4.5)
Abacavir + Efavirance + Lamivudin	1 (1.3)	-	1 (1.5)
Daronavir + Ritonavir + Dultegravir	2 (2.5)	-	2 (3.0)
Truvada + Kaletra	1 (1.3)	-	1 (1.5)
Dultegravir + Lamivudin + Tenofovir	2 (2.5)	1 (8.3)	1 (1.5)
Truvada + Nevirapin	2 (2.5)	-	2 (3.0)
Kubavir + Efavirance	1 (1.3)	-	1 (1.5)
Continuous variables			
Age(year)	41.14 ± 5.64	41.3 ± 6.9	41.7 ± 5.4
Time since HIV diagnosis (year)	8.45 ± 5.72	10.1 ± 5.1	7.9 ± 5.08
Treatment duration (year)	7.79 ± 4.76	8.9 ± 3.7	7.4 ± 4.7
CD4 (Cells/μL)	611 ± 352.9	646 ± 235	619 ± 381
Ca (mg/dl)	9.4 ± 0.34	9.3 ± 0.49	9.4 ± 0.32
P (mg/dl)	3.4 ± 0.62	3.5 ± 0.6	3.4 ± 0.61
Cr (mg/dl)	0.9 ± 0.21	0.94 ± 0.24	0.93 ± 0.21
PTH (pg/ml)	47 ± 18.7	53 ± 19.9	47 ± 18
Hb (g/dl)	14.42 ± 1.95	14 ± 3	14 ± 1
ESR (mm/h)	6(5.0-10.25)	10(5.0-11.75)	6(5.0-10.75)
Alkph (U/L)	101 ± 34	117 ± 41	98 ± 31
TSH(mIU/ml)	2.1(1.5–3.2)	2.15(1.53–3.15)	2.3(1.5–3.2)
Ft4(pmol/L)	16.8 ± 6.3	16.4 ± 1.6	16.2 ± 3.4
Testosterone in male (ng/ml)	5.27 ± 2.20	5.5 ± 3.99	3.05 ± 2.88
Estradiol in female (pg/ml)	68.25(22.75-130.78)	34(20)	62.6(72.5)
Estradiol in male (pglml)	32.4(26.0-39.9)	NA	NA
LH (IU/L)	7.1(5.0-11.1)	7.1(5.98–8.83)	7.8(5.2–11.1)
Vitamin D (ng/ml)	58.37 ± 26.28	54 ± 22	58 ± 25
FBS (mg/dl)	94 ± 13	91 ± 13.5	94 ± 12
BMI (kg/m2)	25.7 ± 4.5	23 ± 4	26 ± 4.8
Femoral Neck T-score	-0.54 ± 1.18	NA	NA
Femoral Neck Z-score	-0.4 ± 1	NA	NA
Femoral Neck BMD (g/cm2)	0.79 ± 0.13	NA	NA
Total Hip Z-score	-0.005 ± 0.92	NA	NA
Total Hip T-score	0.19 ± 1.12	NA	NA
Total Hip BMD (g/cm2)	0.96 ± 0.14	NA	NA
Lumbar Z-score	-0.66 ± 1.28	NA	NA
Lumbar T-score	-0.65 ± 1.2	NA	NA
Lumbar BMD (g/cm2)	0.98 ± 0.15	NA	NA

Data are indicated as Mean ± SD, Median (IQR), or N (%)

Abbreviations: BMD, Bone mineral density; BMI, Body mass index; NA, Not applicable; CD4, Cluster of differentiation 4; Ca, Calcium; P, Phosphorus; Cr, Creatinine; PTH, Parathyroid hormone; Hb, Hemoglobin; ESR, Erythrocyte sedimentation rate; Alkph, Alkaline phosphatase; TSH, Thyroid-stimulating hormone; Ft4, Free thyroxine; LH, Luteinizing hormone; FBS, Fasting blood sugar

P=0.005), total hip BMD (r = -0.29, P=0.008), and lumbar BMD (r = -0.24, P=0.03). Lower femoral neck (r = -0.26; P=0.01) and total hip (r = -0.29; P=0.01) regions of BMDs are associated with higher levels of PTH. Lower lumbar BMD is correlated with higher Alkph levels (r = -0.22; P=0.04). Estradiol levels in females have a correlation with lumbar BMD (r=0.36; P=0.04); doing so in males for the femoral neck (r=0.41; P=0.005) and total hip (r=0.29; P=0.05) regions. Higher LH in females negatively impacts lumbar BMD (r = -0.5; P=0.004). Hemoglobin with the lumbar BMD and BMI with that of all areas showed a positive correlation (Table 2). To better visualize these correlations, see Fig. 1.

Time since diagnosis of HIV was 8.54±5.72 years, and according to the analysis, with increasing time since diagnosis of HIV, bone density decreased in all 3 areas, with none of the associations being significant (all P-value>0.05). The mean duration of HIV treatment in the population under study was reported at 7.79±4.76, and with the increase in the duration of receiving the treatment, bone density also decreased, but this association was not significant (all P-values>0.05). The mean CD4 level in the patients was calculated as 352.9±611, and no correlation was observed with bone density in the 3 mentioned areas (all P-values>0.05). BMI showed a positive trend toward association with lumbar low BMD (OR [95% CI]=1.17 [0.99–1.38]; P=0.07). Higher testosterone levels were significantly associated with lower odds of lumbar low BMD in patients with HIV (OR [95%CI]=0.79 [0.62–0.96]; P=0.02). (Table 3). The mean BMD in the femoral neck area in patients with detectable and undetectable viral loads was 0.76±0.07 and 0.79±0.14, respectively, but no significant difference was seen (P-value=0.59). Mean BMD in the total femur area was reported at 0.94±0.12 and 0.96±0.15, respectively, in patients with detectable and undetectable viral loads; however, this association was not statistically significant (P-value=0.06). No significant association was observed between the BMD in the lumbar region and the HIV viral load.

Six variables were deemed eligible to enter multivariable logistic regression analysis, including male gender, duration of HIV infection, Ca, Alkph, testosterone, and BMI. However, none of the variables were statistically significant for predicting the low BMD in the lumbar region.

Discussion

The present study aimed to assess BMD in patients with HIV and explore potential factors influencing BMD in various anatomical regions. The findings shed light on several associations between biochemical parameters, hormonal levels, treatment duration, and BMD in different bone regions of the study. Our main findings entail

Table 2 Correlation coefficient of variables and BMD of different regions

Variable	Femoral Neck BMD		Total Hip BMD		Lumbar BMD	
	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value	Correlation coefficient	*P*-value
Age (year)	0.00	0.99	0.006	0.96	0.03	0.81
Time since HIV diagnosis (year)	-0.07	0.54	-0.06	0.55	-0.18	0.10
BMI (kg/m2)	0.29	0.008*	0.31	0.005*	0.30	0.009*
Treatment duration (day)	-0.05	0.65	-0.02	0.84	-0.11	0.30
CD4 (Cells/μL)	-0.05	0.64	-0.02	0.84	0.01	0.92
Ca (mg/dl)	0.06	0.58	0.15	0.19	0.20	0.07
P (mg/dl)	-0.31	0.005*	-0.29	0.008*	-0.24	0.03*
Cr (mg/dl)	0.05	0.68	0.19	0.08	0.00	0.99
ESR (mm/h)	-0.04	0.71	-0.05	0.65	-0.17	0.13
PTH (pg/ml)	-0.26	0.01*	-0.29	0.01*	-0.21	0.07
Hb (g/dl)	0.24	0.03*	0.27	0.02*	0.23	0.04*
Alkph (U/L)	0.05	0.97	-0.04	0.69	-0.22	0.04*
TSH (mIU/ml)	-0.006	0.61	-0.01	0.92	-0.07	0.51
Ft4 (pmol/L)	-0.005	0.96	0.016	0.89	0.04	0.74
Testosterone in male (ng/ml)	0.06	0.69	0.06	0.70	-0.06	0.68
Estradiol in female (pg/ml)	0.07	0.72	0.22	0.23	0.36	0.04*
Estradiol in male (pg/ml)	0.41	0.005*	0.29	0.05*	0.13	0.38
LH in male (IU/L)	0.09	0.54	0.06	0.66	-0.02	0.91
LH in female (IU/L)	-0.05	0.8	-0.07	0.72	-0.5	0.004*
Vitamin D (ng/ml)	0.07	0.55	0.07	0.55	0.13	0.26
FBS (mg/dl)	0.00	0.96	-0.07	0.56	-0.14	0.22

Abbreviations: BMD, Bone mineral density; BMI, Body mass index; HIV, Human immunodeficiency virus; CD4, Cluster of differentiation 4; Ca, Calcium; P, Phosphorus; Cr, Creatinine; ESR, Erythrocyte sedimentation rate; PTH, Parathyroid hormone; Hb, Hemoglobin; Alkph, Alkaline phosphatase; TSH, Thyroid-stimulating hormone; Ft4, Free thyroxine; LH, Luteinizing hormone; FBS, Fasting blood sugar

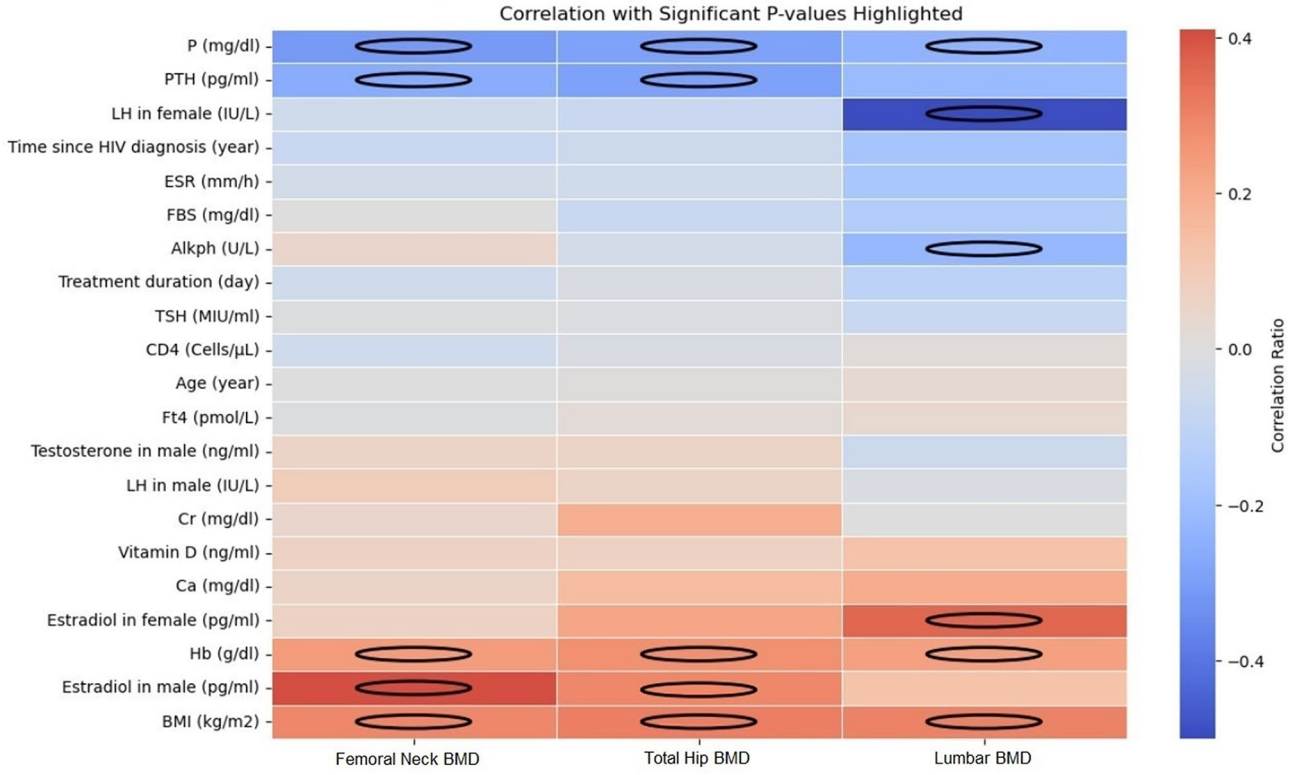

Fig. 1 Heatmap of the correlation coefficients of dependent variables and sites of BMD, with marked significant *p*-values

a significant proportion of patients with HIV presenting with low BMD, especially in the lumbar region. Testosterone was the only factor that was proven to lower the odds of lumbar low BMD in patients with HIV.

Decreased bone mineral density is one of the common complications in patients with HIV, and the treatment of the primary disease causes an increase in osteopenia and osteoporosis compared to the normal population [32, 33]. In untreated patients with HIV, BMD decreases as a result of the direct effects of the virus, namely through systemic inflammation and bone remodeling, and proteins produced by the virus, which not only increase the activity of osteoclasts but also disrupt bone formation by stimulating bone apoptosis [34, 35]. During the first year or two after beginning antiviral therapy, the largest reduction in bone density is observed [11]. The transient decline in bone mineral density during the initiation of antiviral treatment is due to the reconstruction of the immune system, increased bone resorption (increased functions of the RANKL/OPG pathway), and the effect of some drugs such as tenofovir on bone metabolism [36, 37]. According to a meta-analysis, ART-treated patients had a two-fold higher prevalence of osteopenia/osteoporosis than did controls [18]. Another meta-analysis's most significant findings were that individuals with HIV had lower BMD in the lumbar spine and hip, as well as a higher incidence of fractures overall, fragility fractures, vertebral fractures, and wrist fractures than controls [38]. They also found that lumbar spine BMD was significantly lower in patients who are HIV positive compared to controls in age- and BMI-matched studies. HIV infection and low BMI are separate risk factors for low bone mass, as we found a statistically significant correlation between BMI and lumbar BMD. The logic of the importance of adequate nutrition, including calcium and vitamin D intake, for good bone health may be applied [39]. It has been reported that the burden of osteoporosis in patients with HIV increases compared to the control group, especially in the fifth decade of life [40]. In our study, the prevalence of low bone density based on the Z score measured in different areas was 15% in the lumbar spine area and 3.75% in the femoral neck area.

In men, testosterone is effective in the BMD due to the androgen receptors present in the cortical and trabecular parts of bones, and as a result, the decrease in testosterone causes the loss of bone tissue in men [41]. A study showed that testosterone use in men with HIV is associated with higher BMD. In men with HIV with virologic suppression (HIV RNA < 50 copies/mL), testosterone was significantly associated with a higher BMD T-score at the lumbar spine, total hip, and femoral neck compared with nonusers [42]. In our study, there was a significant relationship between the testosterone level in men and bone density in these patients. However, we did not find an

Table 3 Univariable logistic regression models evaluating predictors of low BMD of the lumbar region

Variable	OR	95%CI	*P*-value
Male	0.25	0.05–1.25	0.09
Smoking	1.05	0.28–3.85	0.95
Alcohol	1.5	0.28–8.11	0.64
Detectable viral load	0.46	0.05–4.01	0.49
Age (year)	1.01	0.91–1.13	0.83
Time since HIV diagnosis (year)	0.92	0.82–1.04	0.17
Treatment duration (year)	0.93	0.81–1.07	0.29
CD4 (Cells/μL)	1.00	0.998–1.001	0.81
Ca (mg/dl)	3.3	0.64–17.32	0.15
P (mg/dl)	0.8	0.29–2.21	0.67
Cr (mg/dl)	0.89	0.05–14.86	0.94
PTH (pg/ml)	0.98	0.96–1.02	0.31
Hb (g/dl)	1.08	0.8–1.45	0.64
ESR (mm/h)	0.98	0.95–1.01	0.16
Alkph (U/L)	0.99	0.97-1.00	0.09
TSH (mIU/ml)	1.02	0.92–1.13	0.75
Ft4 (pmol/L)	0.98	0.81–1.19	0.85
Testosterone (ng/ml)	0.79	0.62–0.96	0.02
Estradiol (pg/ml)	1.02	0.99–1.04	0.23
LH (IU/L)	1.02	0.96–1.08	0.49
Vitamin D (ng/ml)	1.01	0.98–1.03	0.59
FBS (mg/dl)	1.02	0.97–1.08	0.38
BMI (kg/m2)	1.17	0.99–1.38	0.07

Abbreviations: BMD, Bone mineral density; BMI, Body mass index; OR, Odds ratio; CI, Confidence interval; HIV, Human immunodeficiency virus; CD4, Cluster of differentiation 4; Ca, Calcium; P, Phosphorus; Cr, Creatinine; PTH, Parathyroid hormone; Hb, Hemoglobin; ESR, Erythrocyte sedimentation rate; Alkph, Alkaline phosphatase; TSH, Thyroid-stimulating hormone; Ft4, Free thyroxine; LH, Luteinizing hormone; FBS, Fasting blood sugar

association for female hormones. Research suggests that in postmenopausal women infected with HIV, menopausal stage and HIV infection are independent predictors of lower BMD, particularly in the lumbar spine and hip. Lower BMD was linked to postmenopausal status, older age, lower BMI, and use of glucocorticoids in a systematic review of research including women positive for HIV [43]. The impact of HIV on BMD in women is compounded by the additional consequences of estrogen withdrawal and deficiency, which can lead to metabolic alterations similar to those caused by HIV [44].

Our study has shown that the mean time since of diagnosis of HIV among affected individuals can range from 1 to 6 years, and low CD4 cell count is a predictor of a low BMD [45]. Additionally, the initiation of antiretroviral therapy is associated with a 2–6% decrease in BMD over the first 2 years, similar in magnitude to that sustained during the first 2 years of menopause [10]. Furthermore, a study found that BMD was not correlated with viral load, CD4 cell count, or the duration of therapy, but was correlated with weight and the use of protease inhibitor therapy [46]. While our study too did not find an association for the above-listed variables, the reasons for these associations reported by other studies can be multifactorial. Low CD4 cell counts and the duration of HIV disease can impact bone health due to the direct effects of the virus on bone metabolism. Additionally, the use of certain antiretroviral therapies, such as protease inhibitors, and the associated weight changes can further contribute to decreased BMD [47].

Limitations

However, several limitations warrant consideration. The study's cross-sectional design impedes establishing causality, necessitating longitudinal studies to elucidate temporal relationships between HIV-related variables and BMD alterations. Moreover, the relatively small sample size may hinder not only the power of the study to show correlation but also the generalizability of the findings to broader HIV populations.

Further implications

This study provides valuable insights into the intricate relationship between biochemical, hormonal, and clinical factors and BMD in patients with HIV. Future research endeavors should focus on longitudinal studies with larger cohorts to validate these findings and delineate the dynamic interactions influencing bone health in individuals living with HIV. Such efforts are pivotal for devising targeted interventions aimed at preserving bone density and mitigating osteoporosis-related complications in this patient population. A critical aspect of this study lies in comparing the prevalence of low bone density in HIV-positive individuals with non-HIV groups to clarify the need for targeted investigations in younger populations. These findings raise questions about whether individuals under 50 living with HIV should undergo routine bone density screening to identify early risks of osteopenia or osteoporosis.

Conclusion

The study investigated the impact of disease and treatment duration on BMD in patients with HIV. Higher BMI and hemoglobin levels were positively associated with better BMD in the femoral neck, total hip, and lumbar spine, while elevated phosphorus, parathyroid hormone, and alkaline phosphatase levels were linked to lower BMD in these areas. Additionally, estradiol levels in men and women positively correlated with BMD, with estradiol in men linked to the femoral neck and total hip and in women linked to the lumbar spine. Conversely, luteinizing hormone in women was negatively correlated with lumbar BMD. The findings highlight the complexity of factors influencing BMD in patients with HIV.

Abbreviations

AIDS Acquired Immunodeficiency Syndrome
Alkph Alkaline Phosphatase

ART	Antiretroviral Therapy
BMD	Bone Mineral Density
BMI	Body Mass Index
Ca	Calcium
Cr	Creatinine
CD4	Cluster of Differentiation 4
DXA	Dual-Energy X-ray Absorptiometry
FBS	Fasting Blood Sugar
Ft4	Free Thyroxine
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
LH	Luteinizing Hormone
P	Phosphate
PTH	Parathyroid Hormone
RNA	Ribonucleic Acid
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
TSH	Thyroid-Stimulating Hormone
WHO	World Health Organization

Author contributions
M.H. and N.F. contributed to the study conception and design and supervised the project. S.S. and A.A analyzed the data and wrote the first draft of the manuscript. Z.F. and M.H. and A.A. gathered the data, did assessments, contributed to the study design, and edited the manuscript. M.H. and N.F. and N.S. and L.A. contributed to the study design, revised the manuscript, and drew tables. All authors commented on previous versions of the manuscript and revised it. All authors read and approved the final manuscript. A.A. and M.H. contributed equally to this work.

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Data availability
The data that support the findings of this study are available from the corresponding author (N.S.) upon reasonable request.

Declarations

Ethics approval and consent to participate
The Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1400.139) approved and verified the study protocol which was conducted in accordance with the Declaration of Helsinki.

Consent to participate
An informed consent signed by all the participants in the study was obtained.

Consent to publish
Not applicable.

Competing interests
The authors declare no competing interests.

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