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HIV infection and bone disease: a review of the literature

D. Castronuovo[1], M.R. Pinzone[1], S. Moreno[2], B. Cacopardo[1], G. Nunnari[1]

[1]Division of Infectious Diseases, Department of Clinical and Experimental Medicine, Garibaldi Nesima Hospital, University of Catania, Catania, Italy

[2]Department of Infectious Diseases, Ramon y Cajal Hospital, Madrid, Spain

ABSTRACT:

Highly active antiretroviral therapy (HAART) has changed Human Immunodeficiency Virus (HIV) infection into a chronic disease. HIV-infected patients live longer now, hence, several non-AIDS-associated morbidities are emerging.

The prevalence of bone disease is high among HIV-infected patients compared to uninfected subjects. HAART, chronic inflammation, the virus itself and traditional risk factors have been suggested to contribute to bone remodeling and loss.

In the present review we report the current data from the literature regarding risk factors for low bone mineral density and fractures in HIV-positive patients.

Key words: HIV, Bone disease, Osteoporosis, Fractures, DXA, HAART, Inflammation.

INTRODUCTION

Highly active antiretroviral therapy (HAART) has changed Human Immunodeficiency Virus (HIV) infection into a chronic disease, with extended life expectancy especially in the absence of comorbidities and for patients with good access to medical care[1]. Since HIV-infected patients are living longer, several aging-related non-AIDS-associated morbidities, such as diabetes mellitus, malignancies, cardiovascular disease, osteoporosis, osteopenia and fragility fractures are becoming more prevalent[2-20]. However, HAART cannot eradicate HIV infection[21-34].

Osteoporosis is a skeletal disorder characterized by bone remodeling, low bone mass and microarchitectural changes of bone tissue, with increased bone fragility and fractures[1]. Bone mineral density (BMD) is measured by dual X-ray absorptiometry (DXA), to identify patients at high risk of fractures[1].

The World Health Organization has defined reduced BMD into two categories. Osteoporosis is characterized by BMD less than 2.5 standard deviations of the mean BMD of a sex-matched, young healthy population, i.e. a T-score less than <-2.5. Osteopenia is defined as bone loss with a T-score between -1 and -2.5. These categories were created for postmenopausal women, although they are now often used for the adult population[1].

Osteoporosis has become an important cause of morbidity and mortality in the HIV-infected population. It has been related to traditional risk factors, such as smoking, alcohol use, opiate use, physical inactivity, low body weight, hypogonadism and vitamin D deficiency, but also to chronic immune activation and antiretroviral drugs[35,36-76].

In the present review we report the current data from the literature regarding risk factors for low bone mineral density and fractures in HIV-positive patients.

Pathogenesis of bone disease

The etiology of osteoporosis is multifactorial. The main risk factors remain the same as in the general population and play the same role, although they may be more prevalent in HIV-infected people (low body mass, sedentary lifestyle, smoking, alcohol abuse, glucocorticoid therapy,

CORRESPONDING AUTHOR: G. NUNNARI, MD, PH.D; E-MAIL: GNUNNARI@HOTMAIL.COM

low consumption of calcium and vitamin D)[37-39]. In addition, immune dysfunction and persistent inflammation, as well as antiretroviral drugs, have been reported to negatively impact on bone health[37]. Cytokines and other soluble immune factors play a major role in the physiology of osteoblast maturation and osteoclastic bone resorption[37-40]. In healthy subjects, several factors regulate bone metabolism, including the neuroimmune network and the neuroendocrine-immune system (e.g., adrenocorticotropin hormone; parathyroid hormone (PTH) and calcitonin)[37-40].

The PTH pathway is particularly important, as it modulates the production of the proinflammatory cytokine interleukin (IL)-6 and the Receptor Activator of Nuclear Factor kappa-B Ligand (RANKL)[41,42].

In untreated HIV disease, bone resorption and bone formation are uncoupled due to both direct viral effects and proinflammatory pathways. HIV viral proteins, like vpr and gp120, promote osteoclast activity, whereas p55-gag suppresses osteoblast activity and increases osteoblast apoptosis, *in vitro*[41-43]. Furthermore, tumor necrosis factor (TNF)-α and IL-6, and other proinflammatory molecules stimulate osteoclastogenesis and bone resorption[44,45]. Moreover, high HIV RNA viral load and T-cell activation have been correlated with elevated levels of RANKL, which usually lead to osteoclast formation and increased bone turnover[46,47]. Moreover, interferon-γ, whose levels are remarkably downregulated in advanced HIV infection, is a physiological inhibitor of RANKL signaling[48]. Osteopontin (OPN), produced by osteoblasts and several immune cells, including macrophages, neutrophils, dendritic cells and T and B cells, has chemotactic properties and may induce T-cell activation. OPN-induced immune pathways interfere with osteogenesis, immune regulation[49], osteoclast activity and TH1 and TH17 cells, *in vitro* and in rats[50].

A recent study showed a relationship between bone mass turnover and BMD, as well as bone marrow (BM) mesenchymal stem cells (MSCs) and HIV proteins Tat and Nef. In BM, MSCs are constantly recruited and subsequently differentiated into osteoblasts. They hypothesized that in antiretroviral treatment (ART)-naive patients, Tat and Nef may represent critical pathogenic elements. The in vitro data showed that Tat and Nef could reduce the number of available precursors by inducing MSC senescence, through reducing proliferative activity associated with increased oxidative stress and mitochondrial dysfunction. These results offer new insights into the pathophysiological mechanisms of decreased BMD in HIV-infected patients[70,73].

Iannotti et al reported an association between osteoporosis and cardiovascular disease. In this study, the authors evaluated the presence and distribution of abdominal aortic calcifications (AAC) and its correlation with bone mineral density (BMD) and vertebral fractures (VF) in a cohort of HIV-positive patients. AAC was identified using the AAC-8 score, which estimates the total length of calcification of the anterior and posterior aortic walls in front of vertebrae L1-L4. Low BMD was defined by T-score or Z-score <-1 at lumbar spine or femoral neck. VF were identified by morphometric analysis of X-ray and were defined by the "spine deformity index" (SDI) ≥1 according to semiquantitative method by Genant. They performed lateral spine X-ray and DXA on 280 asymptomatic HIV-positive patients. AAC≥1 was present in 65 patients (23.2%); of these 15 patients showed moderate/severe calcifications (AAC>2). Low BMD was found in 163 patients (58.2%) and VF (SDI≥1) in 47/274 patients (17.1%). The grade of AAC was directly correlated with the grade of SDI (r=0.16; p=0.008): AAC>2 determined a six fold increase in the risk of VF (HR 6.44 [CI 95% 2.21-18.79], p=0.0006). AAC≥1 predicted VF independently from BMD, vitamin D status and bone turnover marker. In conclusion, they demonstrated that AAC was a strong predictor of both low BMD and VF, irrespective of factors involved in bone formation. In addition, the grade of AAC was directly correlated with the grade of VF[74].

HAART AND BONE LOSS

Several antiretroviral regimens have been associated with bone loss, although the mechanisms and degree of BMD loss depend on antiretroviral drug associations[37].

HAART initiation has been associated with a loss of BMD (2-6%), regardless of the regimen, followed by a steady state and then an increase in BMD within 1-2 years. A meta-analysis compared HAART-naive and HAART-treated patients, showing a 2.5-fold increase in the prevalence of low BMD in the treated population, after adjusting for other risk factors for osteoporosis[35]. Initiating with tenofovir (TDF) and/or protease inhibitor (PI)-based regimens, in comparison with non-nucleoside reverse transcriptase inhibitors (NNRTI), led to a higher decrease of BMD[51,52].

TDF has been associated with bone demineralization[53,54], nephrotoxicity, epithelial damage in the proximal tubule and hypophosphatemia, which may be responsible in turn for increased PTH levels and bone resorption. A retrospective study reported that foot fractures were more frequent in HIV-infected patients treated with TDF than non-TDF-containing HAART.

The ASSERT study randomized 385 HAART-naïve patients to receive either abacavir-lamivudine (ABC/3TC) or tenofovir-emtricitabine (TDF/FTC) with efavirenz (EFV)[56]. Bone turnover markers increased in both groups over the first 6 months and then stabilized, with greater increase in the group receiving TDF/FTC and EFV at 24 weeks[56]. Analogously, TDF/FTC-treated subjects had significantly greater decrease in spine and hip BMD than those receiving ABC/3TC at week 96 in a study by McComsey et al; moreover, a greater BMD loss at the spine at 96 weeks was found among patients receiving ATV/ritonavir (r) compared with EFV[57].

Another study compared HAART-naive patients treated with zidovudine (ZDV)/3TC/lopinavir (LPV)/r or nevirapine (NVP)/LPV/r; after initiation of HAART a rapid decrease in femoral neck and lumbar spine BMD was found in both groups[58]. Lumbar spine bone loss stabilized in the second year of treatment, whereas continuous bone loss in the femoral neck was observed in the ZDV/3TC/LPV/r group [58]. Furthermore, markers of bone formation and resorption increased in all patients, indicating augmented bone turnover. Enhanced osteoclastogenesis has been associated with both ZDV and 3TC[58,59].

A recent study compared BMD changes over 96 weeks in 328 HIV-infected, treatment-naive individuals randomized equally to tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) plus atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), or raltegravir (RAL). The authors also assessed if baseline levels of inflammation markers and immune activation, like C-reactive protein, interleukin 6, soluble CD14, markers of CD4(+) T-cell senescence and CD4(+) T-cell activation, were independently associated with BMD loss. They showed that BMD loss was similar in the protease inhibitor (PI) arms (spine -4.0% in the ATV/r group *vs*. -3.6% in the DRV/r [*p*=0.42]; and the hip: -3.9% in the ATV/r group *vs*. -3.4% in the DRV/r group [*p*=0.36]), but lower among those receiving RAL (spine: -3.8% *vs*. -1.8% [*p*<0.001]; hip: -3.7% *vs*. -2.4% [*p*=0.005]). In multivariable analyses, higher baseline concentrations of highly-sensitivity C-reactive protein, interleukin 6, and soluble CD14 were associated with greater total hip BMD loss, whereas markers of CD4(+) T-cell senescence and CD4(+) T-cell activation were associated with lumbar spine BMD loss[69].

In the recent GUSTA study, a non-inferiority study of therapeutic switch to maraviroc+darunavir/ritonavir (MVC+DRV/r) 300/800/100 mg QD vs the continuation of previous triple cART in patients with stable virological suppression, BMD changes have also been monitored. In this two-arm, prospective, multicenter, 1:1 randomized controlled trial, DXA and bone metabolism biomarkers were evaluated at baseline and week 48. The majority of patients (70.4%) were on tenofovir, 63% was on a PI-based regimen and 14.8% on an NNRTI-based regimen. Mean proximal femur BMD from baseline increased over 48 weeks by 2.06% (SD 2.24) in the study arm and decreased by -2.77% (SD 4.63) in the control arm (*p*=0.003). The change over 48 weeks in proximal femur T-score was significantly different between the study (+0.11, SD 0.22) and control arm (-1.14, SD 0.27, *p*=0.016). Also, the changes in total alkalin phosphatase (-20 U/L *vs*. -1.5, *p*=0.003) was significant between the two groups. After adjusting for time from HIV diagnosis and years of ART, being in the study group was the only factor associated with higher mean percentage change from baseline femoral BMD (MVC+DRV/r +4.83, *p*=0.044). The study demonstrated a significant improvement in femoral BMD and T-score after treatment simplification with MVC+DRV/r[72].

GUIDELINES FOR MONITORING BONE DISEASE

EACS guidelines recommend screening for all causes of low BMD[60]. Laboratory work up includes complete blood count, calcium, phosphate, albumin, creatinine, 25-hydroxyvitamin D as well as PTH, thyroid-stimulating hormone and 24-hour urine collection. For patients on TDF, urinary phosphorus levels should also be evaluated. The expert panel also suggests checking testosterone levels in men and estradiol, prolactin, follicle-stimulating hormone and luteinizing hormone in premenopausal women with amenorrhea[60].

New bone turnover biomarkers like bone-specific alkaline phosphatase (BAP) and tartrate-resistant acid phosphatase (TRAP), have been evaluated in a recent study. In particular, the authors assessed the association of bone turnover biomarkers with blood levels of alkaline phosphatase (ALP), BAP, osteocalcin (OC), TRAP and PTH in HIV-1 infected men receiving ART. The participants of this study where divided into three groups: 35 HIV-1 infected men on ART, 35 HIV-1-infected men not on ART, and 34 uninfected men. Multivariate analyses showed significant differences in mean TRAP and BAP concentrations between the three groups. A strong correlation between blood levels of BAP and TRAP (r=0.570, *p*=0.0004) and between BAP and PTH (r=0.436, *p*=0.0098) were observed for HIV-1 infected men on ART. The authors concluded that serum levels of TRAP and BAP represent superior laboratory tools for assessing the hyperactivity of osteoclasts, osteoblasts and bone loss in HIV-1 infected individuals receiving ART[71].

The National Osteoporosis Foundation recommends osteoporosis screening with DXA for all women aged >65 years and men aged >70 years, regardless of clinical risk factors, and for adults aged >50 with additional risk factors for osteoporosis[35].

Fracture Risk Assessment Tool (FRAX) algorithm (http://www.shef.ac.uk/FRAX/) is used to calculate 10-year fracture risk by integrating information coming from patients' risk factors for osteoporosis and BMD. However, FRAX algorithm has not been formally validated for HIV-positive patients, because it may underestimate fracture risk and may not discriminate between patients who have osteopenia and those who have not[61,62]. TDF should be used carefully in patients with low trauma or atraumatic fractures or very low BMD, due to the association with proximal tubule dysfunction[60].

Recently, 34 HIV specialists from 16 countries contributed to a project, whose primary aim was to provide guidance on the screening, diagnosis, and monitoring of bone disease in HIV-infected patients. As for the evaluation of the risk of fragility fracture, the authors recommended to use FRAX without DXA in all HIV-infected men aged 40-49 years and HIV-infected premenopausal women aged ≥40 years. They suggested that DXA should be performed in men aged ≥50 years, postmenopausal women, patients with a history of fragility fracture, patients receiving chronic glucocorticoid treatment, and patients at high risk of falls. Moreover, they suggested to avoid TDF or boosted PI in at-risk patients. Finally, dietary and lifestyle management strategies for high-risk patients should be reinforced and anti-osteoporosis treatment initiated, if necessary[68].

TREATMENT

Screening and treatment of secondary causes of low BMD are highly recommended by expert consensus panels[60]. Pharmacologic treatment for osteoporosis should be considered for postmenopausal women and men aged >50 years with fragility fractures or a T-score of the hip, femoral neck or lumbar spine ≤-2.5; if the 10-year probability of hip fracture is ≥3% or the 10-year risk for major

osteoporosis-related fractures is ≥20% using the FRAX score, osteoporosis treatment has to be evaluated[37]. Calcium and vitamin D intake should be estimated before treatment, (recommended daily intake: 1000-1500 mg of calcium and 800-1000 IU of vitamin D)[63]. Thirty minutes of weight-bearing (i.e. jogging and walking) and muscle-strengthening exercise at least 3 days a week are also recommended, as such exercise may increase bone density[60]. Smoking cessation and limitation of alcohol intake are also advised[60]. The optimal vitamin D replacement regimen remains to be established: many studies suggest to reach a target 25OHD range of 30-50 ng/mL[60]. Vitamin D can be replaced by vitamin D2 (ergocalciferol) or the more bioavailable vitamin D3 (cholecalciferol)[64].

Alendronate, a bisphosphonate that inhibits osteoclast-mediated bone resorption, has been approved for the treatment of osteoporosis in men and women[64-66]. In the ANRS 120 Fosivir trial, enrolling HIV-infected patients with a T-score <-2.5 at the lumbar spine and/or total hip, patients were randomized to receive either extended-release alendronate 70 mg weekly or placebo for 96 weeks; all the patients also received daily calcium carbonate (500 mg) and vitamin D (400 IU)[66]. Alendronate improved BMD in HIV-infected patients on HAART[66]. In another double-blind, randomized, placebo-controlled trial, the authors evaluated the effects of two annual 4-mg doses of intravenous zoledronate in a cohort of 43 HIV-infected men with BMD T-score <-0.5. The authors found that the effects of zoledronate lasted for at least 5 years after the second dose[67]. Considering the increased life expectancy of HIV-infected people, there is a need for clinical trials evaluating the long-term safety and the optimal duration of treatment with bisphosphonates.

CONCLUSIONS

In HIV-infected patients the prevalence of low BMD is higher as compared with the general population, the pathogenesis remains multifactorial but HIV-related risk factors, such as chronic immune activation and antiretroviral toxicities, need to be taken into consideration along with traditional risk factors, such as hypogonadism, smoking and low body weight. Since HIV infection is now a chronic disease, systematic screening and monitoring for bone disease is critical to prevent fractures, in order to improve the quality of life of HIV-infected subjects.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

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