

Bone disease in the setting of HIV infection: update and review of the literature

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Abstract. – The advent of highly active anti-retroviral therapy (HAART) in the mid-1990s has transformed Human Immunodeficiency Virus (HIV) infection into a chronic disease. HIV-infected patients are living longer and are facing several non-AIDS-associated morbidities related with aging, including diabetes mellitus, cardiovascular disease, osteoporosis, osteopenia and fragility fractures.

The prevalence of bone disease is higher among HIV-infected subjects. In addition to traditional risk factors, HAART, chronic inflammation and the virus itself have been suggested to contribute to bone loss in the setting of HIV infection.

In the present review, we summarize the current knowledge about risk factors for low bone mineral density in HIV-positive patients as well as current recommendations for fracture screening and treatment in this specific population.

Key Words:

HIV, HAART, Osteoporosis, Fracture, Bone, Vitamin D.

Introduction

The advent of highly active antiretroviral therapy (HAART) has transformed Human Immunodeficiency Virus (HIV) infection into a chronic disease, with life expectancy close to that of the general population for patients with good access to high quality medical care¹. HIV-infected patients are living longer and are facing several non-AIDS-associated morbidities related with aging, including diabetes mellitus, malignancies, cardiovascular disease, osteoporosis, osteopenia and fragility fractures²⁻³⁷. However, HAART cannot eradicate HIV infection³⁸⁻⁵¹.

Osteoporosis is defined as a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with

a consequent increase in bone fragility and fracture¹. Bone mineral density (BMD) can be measured by imaging modalities, such as dual X-ray absorptiometry (DXA), which helps identifying patients at high risk of fractures¹.

The World Health Organization has grouped reduced BMD into two categories. Osteoporosis is defined as a bone density 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 an intermediate category of bone loss defined as a T-score between 1 and 2.5. Although these categories were created to classify postmenopausal women, they are often applied to other adult populations¹.

Osteoporosis is likely to become an important cause of morbidity and mortality as the HIV-infected population ages. It has been related not only 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 side effects^{52,53}.

In the present review, we summarize the current knowledge about risk factors for low BMD in HIV-positive patients as well as current recommendations for fracture screening and treatment in the setting of HIV infection.

Etiology of Low BMD in HIV Infection

Among HIV-infected patients the etiology of osteoporosis is multifactorial.

Some risk factors are shared with the general population and may be more prevalent in HIV-infected populations, i.e. low body mass, sedentary lifestyle, smoking, alcohol abuse, glucocorticoid therapy, low consumption of calcium and vitamin D⁵⁴⁻⁵⁶. In addition, immune dysregulation and chronic inflammation, as well as antiretroviral drugs, have been shown to negatively impact

bone health⁵⁴. Cytokines and other soluble immune factors are involved in the modulation of osteoblast maturation and osteoclastic bone resorption⁵⁴⁻⁵⁷. Moreover, bone is richly innervated by both autonomic and sensory neurons. In healthy individuals, several factors control bone metabolism, including the neuroimmune network and the neuroendocrine-immune regulatory system (e.g., adrenocorticotropin hormone; parathyroid hormone (PTH) and calcitonin)⁵⁴⁻⁵⁷.

The PTH pathway is especially important, as it regulates the production of the proinflammatory cytokine interleukin (IL)-6 and the Receptor Activator of Nuclear Factor kappa-B Ligand (RANKL)⁵⁸⁻⁵⁹.

In untreated HIV infection, bone resorption and bone formation are uncoupled because of both direct viral effects and proinflammatory mechanisms. *In vitro* studies demonstrated that HIV viral proteins, like vpr and gp120, may promote osteoclast activity, whereas p55-gag is able to suppress osteoblast activity and increase osteoblast apoptosis⁵⁸⁻⁶⁰. In addition, proinflammatory cytokines, like tumor necrosis factor (TNF)- α and IL-6, stimulate osteoclastogenesis and bone resorption⁶¹⁻⁶². High HIV RNA viral load and T-cell activation have been associated with elevated levels of RANKL, which may lead to osteoclast formation and increased bone turnover⁶³⁻⁶⁴. RANKL plasma concentrations have been positively correlated to HIV RNA viral load⁶². Interferon- γ is a physiological inhibitor of RANKL signaling, whose levels are remarkably downregulated in advanced HIV infection⁶⁵. Therefore, a limited capacity to suppress RANKL during HIV infection may lead to increased osteoclast activation and bone resorption. Osteopontin (OPN) is produced by osteoblasts and several immune cells, including macrophages, neutrophils, dendritic cells and T and B cells. In immune metabolism, OPN is endowed with chemotactic properties that promote cell recruitment to inflammatory sites as well as adhesion properties to several integrin receptors which promote T-cell activation, cytokine production and regulation of apoptosis. OPN carries complex molecular and epigenetic regulatory roles in osteogenesis and immune regulation⁶⁶. OPN regulates osteoclast activity and the development of TH1 and TH17 cells. Vikulina et al⁶⁷ showed that bone loss in HIV transgenic rats was associated with an increase in RANKL and a parallel decline in OPG levels, thus leading to increased osteoclastic bone resorption.

Role of HAART in Bone Loss

In addition to the direct and immune-mediated effects of HIV on the skeleton, several antiretroviral regimens have been associated with bone loss, although the mechanisms and degree of BMD loss vary according to the antiretroviral class⁵⁴.

Initiation of HAART has been associated with a marked and clinically significant loss of BMD (2%-6%), regardless of the antiretroviral regimen, followed by stabilization and increase in BMD within 1-2 years after HAART initiation. In a meta-analysis carried out in 2006 to compare HAART-naïve and HAART-treated patients, there was a 2.5 fold increase in the prevalence of low BMD in the treated population, after adjusting for other risk factors for osteoporosis⁵². BMD decrease seems to be higher when initiating tenofovir (TDF) and/or protease inhibitor (PI)-based regimens, in comparison with non-nucleoside reverse transcriptase inhibitors (NNRTI)^{68,69}.

TDF has been associated with bone demineralization^{70,71}. TDF has been shown to cause nephrotoxicity, with epithelial damage in the proximal tubule and hypophosphatemia, which may be responsible in turn for increased PTH levels and bone resorption. In addition, impaired renal function may cause decreased 1- α -hydroxylation of the vitamin D precursor 25-hydroxyvitamin D (25OHD), thus reducing the levels of the active metabolite 1,25-dihydroxyvitamin D (1,25OH₂D)⁶⁸. A retrospective study conducted in Los Angeles showed that foot fractures were more frequent in HIV-infected patients treated with TDF than non-TDF-containing HAART. Median time from TDF initiation until fracture was 2.57 years⁴⁴. The TDF group had higher median plasma concentrations of alkaline phosphatase, PTH, 25OHD and a lower white blood cell count⁷².

The ASSERT study examined 385 HAART-naïve patients who were randomized to receive either abacavir-lamivudine (ABC/3TC) or tenofovir-emtricitabine (TDF/FTC) with efavirenz (EFV)⁷³. Bone turnover markers (osteocalcin, bone specific alkaline phosphatase, procollagen 1 N-terminal propeptide and serum type 1 collagen cross-linked C telopeptide (CTx)) were assessed. 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 weeks⁷³. Analogously, McComsey et al confirmed that TDF/FTC-treated subjects had significantly greater decrease in spine and hip BMD than those receiving ABC/3TC at week

96; in addition, they found greater BMD loss at the spine at 96 weeks among patients receiving ATV/r (r) compared with EFV⁷⁴.

In another study, HAART-naive patients were treated with zidovudine(ZDV)/3TC/lopinavir (LPV)/r or nevirapine(NVP)/LPV/r; in both groups, a rapid decrease in femoral neck and lumbar spine BMD after initiation of HAART was found⁷⁵. Lumbar spine bone loss stabilized in the second year of treatment, whereas progressive bone loss in the femoral neck was observed in the same period only in the ZDV/3TC/LPV/r group⁷⁵. Moreover, markers of bone formation and resorption significantly increased after HAART initiation in all patients, indicating an increase in bone turnover. Both ZDV and 3TC have been shown to enhance osteoclastogenesis, potentially leading to bone loss^{75,76}.

The effects on BMD of new antiretroviral classes, including integrase and entry inhibitors, remain to be established.

Several questions are still unanswered. In fact, the mechanisms leading to an acute decrease in BMD after HAART initiation are unclear; in addition, although a BMD recovery is observed after the first 1-2 years on HAART, the long-term clinical impact of such a BMD loss has not been clarified yet.

Screening for Bone Disease in HIV

Current EACS guidelines recommend to screen and treat secondary causes of low BMD⁶⁰. 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 amenorrhea⁷⁷.

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 osteoporosis⁵².

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 the fracture risk and may not discriminate be-

tween patients who have osteopenia and those who have not^{78,79}. TDF should be used with prudence in patients with low trauma or atraumatic fractures or very low BMD, due to the association with proximal tubule dysfunction⁷⁷.

Treatment

Expert consensus panels suggest screening and treatment of secondary causes of low BMD⁷⁷. Pharmacologic treatment of osteoporosis should be undertaken 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 ; pharmacological treatment should also be considered if the 10-year probability of hip fracture is $\geq 3\%$ or the 10-year risk for major osteoporosis-related fractures is $\geq 20\%$ using the FRAX score⁵⁴.

Prior to treatment, calcium and vitamin D intake should be estimated. Guidelines suggest to increase intake from dietary sources and administer 1000-1500 mg of calcium and 800-1000 IU of vitamin D daily⁸⁰. 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 density⁷⁷. Smoking cessation and limitation of alcohol intake are also advised⁷⁷. The optimal vitamin D replacement regimen is unknown: many studies suggest to reach a target 25OHD range of 30-50 ng/mL⁷⁷. Vitamin D can be replaced by vitamin D2 (ergocalciferol) or the more bioavailable vitamin D3 (cholecalciferol)⁶⁴. Recently, the US Endocrine Society recommended the administration of 1000-2000 IU of vitamin D daily. Larger doses [i.e. 50,000 IU (orally weekly for 8 weeks or 300,000 IU by intramuscular injection every 3 months)] may be required for patients with more severe vitamin D deficiency⁸⁰.

Alendronate is a bisphosphonate which inhibits osteoclast-mediated bone resorption and has been approved for the treatment of osteoporosis in men and women⁸¹⁻⁸³.

The ANRS 120 Fosivir trial examined the effect of alendronate on BMD in HIV-infected patients with a T-score < 2.5 at the lumbar spine and/or total hip⁸³. 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). Alendronate 70 mg weekly for 96 weeks was shown to improve BMD in HIV-infected patients on HAART⁸³. In another double-blind, ran-

domized, 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 antiresorptive effects of zoledronate persisted for at least 5 years after the second dose⁸⁴. Oral bisphosphonates have been associated with esophageal irritation and dyspepsia; even if rare, osteonecrosis of the jaw has been reported in patients receiving bisphosphonates⁵⁴. In addition, chronic suppression of bone turnover with bisphosphonates has been suggested to predispose to fracture in some patients as it may prevent the repair of microdamage to the bone architecture⁵⁴. 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.

Second-line osteoporosis therapies, including estrogen-replacement therapy, the selective estrogen receptor modulator raloxifene for postmenopausal women, as well as the PTH analogue teriparatide, have not been specifically evaluated in the setting of HIV infection.

Conclusions

The prevalence of low BMD is higher among HIV-infected patients in comparison with the general population. The pathogenesis of bone disease is multifactorial and includes traditional risk factors, such as hypogonadism, smoking and low body weight, and HIV-related risk factors, such as chronic immune activation and antiretroviral toxicities. Considering that HAART has transformed HIV infection into a chronic disease, systematic screening for bone disease is crucial to reduce fracture risk and improve the quality of life of HIV-infected subjects.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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