Infect Dis Trop Med 2019; 5: e567

Bone disease in HIV infection: an overview of pathogenesis, clinical manifestations and treatment

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ABSTRACT: Patients with human immunodeficiency virus (HIV) infection have a higher risk of low bone mineral density (BMD) and fragility fracture than the general population, although the etiological mechanisms are poorly known. The aim of this review is to summarize the available literature data about alterations of bone metabolism in HIV-infected patients to assess the impact of HIV infection and highly active antiretroviral therapy (HAART) on the risk of developing osteopenia and osteoporosis and to provide guidance on the screening, diagnosis, and monitoring of bone disease in HIV-positive population.

Keywords: Vitamin D, Bone health, HIV.

INTRODUCTION

Numerous studies demonstrated a high incidence of reduced bone mineral density (BMD) and an elevated prevalence of osteopenia and osteoporosis in both men and women infected with HIV, compared with control groups[1]. In 2014, the Joint United Nations Program on HIV/AIDS (UNAIDS) estimated that approximately 4.2 million people aged 50 years or more worldwide are living with HIV, surviving the infection thanks to combined Anti-Retroviral Therapy (cART). cART success led to the progressive aging of these patients and, as a consequence, the emergence of age-related diseases, including diabetes mellitus, cardiovascular disease, malignancies, osteoporosis, osteopenia and fragility fractures[2-4]. As a matter of fact, in addition to the traditional risk factors for bone disease, cART, chronic inflammation and HIV itself have complex effects on bone turnover in PLWH[2,5]. Moreover, individuals with HIV have a high prevalence of risk factors for low bone mineral density (BMD), such as poor nutrition, low body weight, high rates of tobacco and alcohol use, hypogonadism and hypovitaminosis D[2,5].

The purpose of this paper is to review the current knowledge about altered bone metabolism that may lead to osteopenia and osteoporosis in HIV-infected patients and to provide an overview of current recommendations for evaluation and management of bone disease in this specific population.

BONE LOSS ASSOCIATED WITH NORMAL AGING

The skeleton is continually renewed by the process of homeostatic bone remodeling. Growth hormone and sex steroids (i.e. testosterone and estradiol) are responsible for the growth spurt during adolescence which culminates with BMD peaking during early adulthood; thereafter, the skeleton is continuously remodeled[5]. Osteoclasts are giant multinucleated cells of myeloid origin that resorb bone under the coordinated action of two cytokines, receptor activator of NF-κB (RANKL) and osteoprotegerin (OPG). RANKL is the key effector of osteoclast differentiation and activity, while OPG is a RANKL receptor that moderates its activity and hence

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of bone resorption. Therefore, the ratio of RANKL to OPG is a key determinant of bone resorption in the body[5]. Bone resorption and formation co-exist. Individuals younger than 35 or 40 years completely replace the resorbed bone during the remodeling cycle. However, with age this cycle becomes unbalanced towards resorption, leading to a small deficit at each remodeling site. In fact, aging is accompanied by a slow decline in BMD both in men and women. In women, after menopause bone loss is intensified for a period lasting 4 to 8 years, which leads to a 20-30% loss in trabecular bone and 5-10 % in cortical bone[5]. Men appear to be better protected against age-related bone decay[6].

Bone loss and fractures are the hallmarks of osteoporosis, regardless of the underlying cause. 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 fractures[2]. BMD can be measured by imaging modalities, such as dual X-ray absorptiometry (DXA), which helps identifying patients at high risk of fractures[2]. Osteoporosis is defined as a bone density less than 2.5 standard deviations (SDs) 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[2]. The diagnosis of osteoporosis can also be made when a hip or spine fragility fracture is present, regardless of BMD. A fragility fracture is generally defined as a fracture resulting from trauma with an energy equal to or less than a fall from a standing position[3]. In older populations, the risk of fracture increases by 2- to 3-fold for each SD decrease in BMD below the young normal mean[3].

BONE AND THE IMMUNE SYSTEM

Accumulating data suggest that the immune system and skeletal system are deeply integrated, forming a nexus referred to as the immuno-skeletal interface (ISI)[5]. The ISI exists as a consequence of shared cells and cytokine effectors that play discrete roles in immune and skeletal functions. Under normal physiological conditions, the immune system secrets bone protective factors such as OPG, which may be lost when the immune system is chronically suppressed (immunosuppression), leading to an accelerated rate of basal bone resorption[5].

HIV INFECTION AND BONE LOSS

Numerous studies have evaluated bone density among patients with HIV infection and have found the prevalence of osteoporosis and osteopenia to be elevated in HIV-infected compared with control groups. A meta-analysis of studies comparing bone mineral density in HIV-infected with non-HIV-infected patients demonstrated a pooled odds ratio of 3.7 for osteoporosis[1].

The pathogenesis of bone disease in HIV infection is multifactorial. Multiple risk factors, such as low body mass, sedentary lifestyle, smoking, alcohol abuse, glucocorticoid therapy, low intake of calcium and vitamin D, are shared with the general population. In addition, immune dysregulation and chronic inflammation, as well as antiretroviral drugs, have been shown to negatively impact bone health[2]. Recently, an ISI disruption characterized by elevated B cell RANKL and diminished OPG has been linked to osteoporosis in HIV infection[7]. Moreover, proinflammatory cytokines, like tumor necrosis factor (TNF) α and IL-6, stimulate osteoclastogenesis[2,8]. High HIV-RNA viral load and T-cell activation have been associated with elevated levels of RANKL, related to an increased bone turnover[2,9]. Interferon-γ (IFN- γ) is a physiological inhibitor of RANKL signaling, which levels are remarkably down-regulated in advanced HIV infection[2]. Therefore, a limited capacity to suppress RANKL during HIV infection may lead to increased osteoclast activation and bone resorption. In healthy individuals, several factors control bone metabolism, including the neuroimmune network and the neuroendocrine-immune regulatory system. 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*, promote osteoclast activity, whereas *p55-gag* is able to suppress osteoblast activity and increase their apoptosis[2].

CART AND BONE LOSS

The introduction of cART has certainly improved the prognosis of HIV patients by reducing their mortality and morbidity but has also revealed some complications related to the therapy[10]. Among these, a greater prevalence of decreased BMD, osteopenia and osteoporosis in the HIV population than the general population has emerged and has been widely studied[10,11]. Although it is extremely effective at reducing HIV viral load and reversing many of the classic manifestations of AIDS, cART intensifies bone loss during disease reversal[7]. Therefore, the skeleton does not improve with antiretroviral therapy but actually undergoes further deterioration with an additional average loss of up to 6% in BMD during the first 2 years of treatment[7].

How ART affects the skeleton has traditionally been considered to be a direct toxic effect on bone cells. However, even before exposure to ART, patients with HIV infection have been recognized to exhibit low BMD[5,7]. More recent studies show that even in newly diagnosed, therapy-naive HIV-infected patients, without any other known causes of osteoporosis, low BMD and high bone resorption are significantly prevalent[10,12]. Moreover, recent studies in which ART is used to treat human hepatitis B virus (HBV) infection demonstrated a little bone loss compared to that in HIV-infected subjects treated with antiretroviral drugs[7]. Although certain ART regimens, particularly those containing tenofovir disoproxil fumarate (TDF), appear to exacerbate bone loss, it is now evident that the majority of HIV-infected individuals already exhibit reduced bone mineral density before

therapy[5]. Studies conducted on transgenic rats demonstrate that severe osteoclastic bone resorption may be a consequence of an imbalance in the ratio of receptor activator of NF-κB ligand to OPG[13]. Indeed, dramatic changes are known to occur within the B cell compartment of HIV-1-infected humans, including declines in resting memory B cell populations and increases in naive and immature/transitional B cells[13]. The relevant B cell populations responsible for elevated RANKL and/or diminished OPG production remain to be determined; however, it is likely that activated mature B cells, a population whose numbers are increased in association with HIV infection, are responsible for RANKL production, whereas resting memory B cells, a population that decreases in HIV infection, may account for diminished OPG production[13]. Furthermore, data confirm that repopulation of immune cells is a common event associated with all classes of HAART and it leads to an inflammatory environment capable of driving significant bone resorption and loss of BMD and mass[5,7]. The recovery of CD4 T cells involves homeostatic reconstitution, a process involving T cell proliferation and expansion to fill available immunological space[7]. Similar processes are involved in CD8 T cell and B cell recovery and are driven in part through cytokine mediated processes. Through costimulatory interactions and cytokine production CD4 T cell subsets further regulate other adaptive immune components including humoral immunity (B cells) and antigen presenting cells including macrophages, dendritic cells and B cells. Therefore, the regeneration and rekindling of adaptive immunity has the potential to produce inflammatory events that may have the capacity to drive osteoclastogenesis and bone loss, as it is characteristic of other inflammatory states[7].

SCREENING AND MONITORING INDIVIDUALS WITH HIV INFECTION AT RISK FOR FRAGILITY FRACTURE

It is appropriate to assess the risk of low BMD and fragility fracture in all HIV-infected adults[14]. Patients with major risk factors for fragility fracture, including a previous history of fragility fracture, receipt of glucocorticoid treatment for >3 months (≥5 mg of prednisone daily or equivalent), or at high risk for falls, should be evaluated with dual-energy X-ray absorptiometry (DXA). In patients without major fracture risk factors, an age-specific evaluation is appropriate[14]. Patients without a major risk factor for fragility fracture, men who are aged 40-49 years and premenopausal women aged ≥40 years should have their 10-year risk of fracture assessed using the Fracture Risk Assessment Tool FRAX score without BMD, with risk assessment performed every 2-3 years or when a new clinical risk factor develops[14]. FRAX algorithm is used to calculate 10-year fracture risk by integrating information coming from patients risk factors for osteoporosis and BMD[2]. However, FRAX algorithm has not been formally validated for HIV-positive patients, because it may underestimate the fracture risk and may not discriminate between patients who have osteopenia and those who have not. TDF should be used with prudency in patients with low trauma or atraumatic fractures or very low BMD, due to the association with proximal tubule dysfunction[2].

EACS 2019 guidelines recommend to screen and treat secondary causes of osteoporosis if a low BMD is found.

BASIC RECOMMENDATIONS FOR ALL HIV-INFECTED PATIENTS

Management strategies for patients at high risk for fragility fracture include dietary and lifestyle changes[14]. An adequate daily intake of dietary calcium is recommended for postmenopausal women and men ≥50 years of age. Daily total calcium intake should be 1000-1500 mg for men 50-70 years of age, or 1200 mg for women ≥51 years of age and men ≥71 years of age. Dietary calcium should be increased as a first-line approach, but calcium supplementation remains a good option for those who cannot achieve adequate calcium intake through diet alone[3,14,15].

As HIV-infected patients are at risk of vitamin D insufficiency or deficiency, vitamin D status should be determined by serum 25-hydroxy vitamin D levels in those with a history of low BMD and/or fracture[14,15].

Supplementary vitamin D should be given to HIV-infected patients with vitamin D insufficiency (<20 ng/mL [<50 nmol/L]) or deficiency (<10 ng/mL [<25 nmol/L]), particularly if the deficiency is associated with compensatory hyperparathyroidism[14]. Vitamin D daily intake from dietary sources should be 800-1000 IU, in order to achieve a serum 25-hydroxy vitamin D level of approximately 30 ng/mL (75 nmol/L) and a suitable maintenance dose administered thereafter to sustain this level[2,14]. Vitamin D deficiency can blunt bone response to bisphosphonate treatment; therefore, the target serum 25-hydroxy vitamin D level of 30 ng/mL should be achieved before initiating therapy with an antiresorptive drug[14,16].

HIV-infected patients with osteopenia/osteoporosis should be reminded to increase regular weight-bearing and muscle-strengthening exercise, avoid tobacco use and excessive alcohol intake[2,14]. Strategies to assess and reduce fall risk, such as checking and correcting vision and hearing, evaluating neurological problems, and referring patients to physical and occupational therapy, are also recommended[3].

THERAPEUTIC MANAGEMENT OF OSTEOPOROSIS IN HIV-INFECTED PATIENTS

Pharmacological treatment should be initiated for HIV-infected patients under the same criteria as those stated for the general population[14]. According to guidelines anti-osteoporosis treatment 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 ≥ 3% or the 10-year risk for major osteoporosis-related fractures is ≥ 20% using the FRAX score[2]. Before initiating anti-osteoporosis treatment, secondary causes of low BMD should be evaluated. Avoidance or discontinuation of medications associated with bone loss (e.g., antiepileptic drugs, proton pump inhibitors, thiazolidinediones, and corticosteroids) should be considered if appropriate alternatives are available[3,14,17].

Bisphosphonates are generally considered first-line therapy for persons with a history of fragility fracture and/or osteoporosis by DXA, as they inhibit osteoclast-mediated bone resorption[3]. Alendronate and zoledronic acid were shown to significantly improved BMD at the lumbar spine, total hip, and trochanter in HIV-infected patients treated for 48 weeks in randomized controlled trials[3,18]. Alendronate improved lumbar BMD and minimized femoral BMD decrease after 52 weeks compared to treatment with vitamin D and calcium alone in patients on HAART with osteopenia/osteoporosis[19]. Patients with HIV infection should receive alendronate 70 mg once weekly (with calcium carbonate 1000 mg/vitamin D 400 IU per day)[2,14,18]. Intravenous zoledronic acid 5 mg yearly can be given as an alternative to alendronate[14]. Treatment duration should be individualized. Bisphosphonate treatment should be reviewed after an initial 3- to 5-year period, because of concerns about the negative effects of long-term suppression of bone turnover (such as osteonecrosis of the jaw and atypical femoral fractures)[14,20]. Several outcomes have been used in the general population to judge the success of anti-osteoporosis treatment, including the lack of definite fractures, or symptoms or signs of possible fracture; maintenance of height (< 1 cm of loss)[14,21]; no change or an increase in BMD measured by central DXA of hip and spine; reduction in serum or urine markers of bone resorption of ≥ 30%; and therapy adherence[14,22-30].

In HIV-infected patients, if BMD continues to decline on oral bisphosphonate therapy, a second-line approach can include intravenous zoledronic acid[14]. Other second-line osteoporosis therapies, including estrogen-replacement therapy, the selective estrogen receptor modulator raloxifene for post-menopausal women, as well as the PTH analogue teriparatide, have not been specifically evaluated in the setting of HIV infection[2]. Data on the effects of bisphosphonates on the risk of fracture in HIV-infected patients are not available[3]. However, considering the increased life expectancy of HIV-infected people, there is need for clinical trials evaluating the long-term safety and the optimal duration of treatment with bisphosphonates.

CONCLUSIONS

The prevalence of low BMD is higher among HIV-infected patients in comparison with the general population[2]. It is clearly demonstrated that the pathogenesis of bone disease in HIV infection is multifactorial, involving traditional risk factors such as low body weight, hypogonadism, and smoking, and HIV-related risk factors such as chronic immune activation and antiretroviral therapy toxicities[2,10]. With the advancing age of individuals living with HIV/AIDS, low bone mineral density associated with HIV infection is likely to collide with the pathophysiology of skeletal aging, leading to increased fracture risk[13]. The role of ART in increasing the incidence of fractures has not been completely established: up to now, data seems to converge on an increased incidence of fractures among HIV-positive patients exposed to therapy than HAART-naive patients, suggesting the role of certain antiretroviral agents, such as tenofovir disoproxil fumarate (TDF) and protease inhibitors (PI), in increasing the risk of fractures. An extensive number of studies evaluated the effect of ART on fracture risk, especially for those patients who also present other risk factors[10,22-30] . A better control of the HIV disease activity seems to be the first goal to reduce the impact on bone caused by the inflammatory background in these patients[10].

The best approach to these patients should provide a detailed assessment of the parameters of bone metabolism including bone turnover markers. In addition, DXA is confirmed to be a useful tool for assessing possible bone mineral density impairment, although, in this particular setting, even moderately reduced bone mass levels may be associated with increased fracture risk. For this reason, it is necessary to define a different T-score threshold associated with an increased fracture risk. Consequently, in these patients it could be important to perform radiographs of the dorso-lumbar spine in order to detect vertebral fractures even in patients with a normal or slightly reduced bone mass[10]. The early detection of patients at a high risk of fractures allow to introduce a bone sparing treatment already in the first phases of the disease, by using wherever possible a low-impact antiretroviral therapy and by monitoring the presence of vertebral fractures [10]. Only when the mechanism for HIV-related versus HAART-related changes can be defined, will we be much closer to designing specific interventions[31].

In conclusion, cART has greatly prolonged life expectancy in HIV-positive patients, transforming the disease into a chronic condition. Fracture risk assessment should be performed in HIV-infected individuals and bone mineral density measured when indicated. Lifestyle measures to optimize bone health should be advised and, in individuals at high risk of fracture, treatment with bisphosphonates considered.

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

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