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Bone Loss Among Women Living with HIV

M. Neale Weitzmann, Ph.D.,

The Atlanta Department of Veterans Affairs Medical Center, 1670 Clairmont Road, Decatur, Georgia, 30033, USA, and Department of Medicine, Division of Endocrinology and Metabolism and Lipids, Emory University School of Medicine, 101 Woodruff Circle, 1305 WMB, Atlanta, Georgia 30322, USA. Tel: (404) 639-9915, Fax: (404) 639-1300

Ighovwerha Ofotokun, M.D. M.S.,

Department of Medicine, Division of Infectious Diseases, Emory University School of Medicine, 49 Jesse Hill Jr Drive, Atlanta, Georgia 30303, USA, and Grady Healthcare System, 80 Jesse Hill Jr Drive SE, Atlanta, Georgia, 30303, USA. Tel: (404) 616-0659; Fax: (404) 616-0592

Kehmia Titanji, Ph.D.,

Department of Medicine, Division of Endocrinology and Metabolism and Lipids, Emory University School of Medicine, 49 Jesse Hill Jr Drive, Atlanta, Georgia 30303, USA. Tel: (404) 616-6306, Fax: (404) 639-1300

Anjali Sharma, M.D. M.S., and

Department of Medicine, Divisions of General Internal Medicine and Infectious Diseases, Albert Einstein College of Medicine, 1300 Morris Park Ave, Block Bldg #305, Bronx, NY, 10461, USA. Tel: (718) 430-2067; Fax: (718) 430-4035

Michael T. Yin, M.D. M.S.

Division of Infectious Diseases, Columbia University Medical Center, Division of Infectious Diseases, 630 West 168th Street, Box 82, New York, NY 10032, USA., Tel: (212) 305-7185, Fax: (212) 305-7290

M. Neale Weitzmann: mweitzm@emory.edu; Ighovwerha Ofotokun: iofotok@emory.edu; Kehmia Titanji: ktitanj@emory.edu; Anjali Sharma: anjali.sharma@einstein.yu.edu; Michael T. Yin: mty4@columbia.edu

Abstract

Clinical data accumulated over the past two decades attests to a significant decline in bone mineral density (BMD) in patients infected by HIV, which does not remit but may actually intensify with antiretroviral therapy (ART). Long generally perceived as an aberration without clinical consequences in relatively young HIV-infected cohorts, recent studies have documented marked increases in fracture incidence in HIV-infected men and women over a wide age continuum. Fractures are associated with chronic pain, crippling morbidity and increased mortality,

Correspondence: M. Neale Weitzmann, Ph.D., 101 Woodruff Circle, 1305 WMB, Atlanta, Georgia 30322, USA. mweitzm@emory.edu, Tel: (404) 639-9915, Fax: (404) 639-1300.

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undermining the gains in quality of life achieved though ART. As bone loss and resulting increases in fracture incidence are a natural consequence of aging, there is now concern regarding the long-term consequences of HIV/ART-associated premature bone loss, given the transition of the HIV/AIDS population into an older age demographic. The development of guidelines for diagnosis and treatment of bone disease within the context of HIV and ART have been an important recent step in raising awareness of the problem and the implications of bone fracture for patient health. Significant progress has also been made in recent years in dissecting the complex and multifactorial mechanisms driving bone loss in HIV/ART, and the role of underlying immunological disruption in skeletal dysmorphogenesis. This review examines recent progress in the field and studies by WIHS-associated investigators, inside and outside of the WIHS cohort, aimed at identifying skeletal abnormalities, quantifying facture incidence, management and understanding underlying mechanisms in people living with HIV in the context of chronic ART.

Keywords

Adiposity; antiretroviral therapy; ART; B cells; bone loss; cART; falls; fracture; HAART; HIV; osteoclasts; osteoporosis; RANKL; T cells; TNF

Introduction

A growth hormone and sex steroid driven growth spurt during puberty leads to a doubling of skeletal mass with bone mineral density (BMD) peaking in early adulthood (around 25–35 years of age) [1]. Thereafter the skeleton undergoes bone remodeling, a regeneration phase that rejuvenates the skeleton throughout life [2]. In principle, remodeling is homeostatic with osteoclasts removing (resorbing) worn bone and osteoblasts synthesizing an equivalent amount of new bone. However, aging in both men and women is accompanied by a slow decline in BMD, as the rate of bone resorption begins to outpace that of bone formation. In women, loss of estrogen at the time of menopause intensifies bone loss for a period of 4 to 8 years, accounting for a 20–30% loss in trabecular (cancellous) bone and 5–10% in cortical (compact) bone [1]. Postmenopausal osteoporosis is the archetypal bone disease of women and ultimately leads to conditions favorable for bone fracture. This menopause-associated accelerated bone loss is compounded by the fact that women typically have reduced skeletal mass due to smaller, thinner bones, resulting in a 2- to 3-fold higher fracture incidence in women compared with men [2]. Ultimately, approximately 50% of women over the age of 50 will suffer a skeletal fracture [3].

Fractures can have devastating consequences, with hip fractures being the most serious and requiring surgical stabilization of the bone. The healing/rehabilitation period can be extensive and in the majority of patients a protracted stay in nursing facilities is necessary. Between 24% and 32% of patients die within a year of suffering a hip fracture [3, [4]. Preventing fracture is thus an important goal in the clinical management of chronic HIV.

Osteoclasts and Bone resorption

Osteoclasts are giant multinucleated cells of hematopoietic (myeloid) origin that resorb bone under the coordinated action of two key cytokines, receptor activator of NF-κB (RANKL)

and Osteoprotegerin (OPG). RANKL is the key effector of osteoclast differentiation and activity. OPG is a RANKL decoy receptor that moderates the activity of RANKL and hence of bone resorption. Thus the ratio of RANKL to OPG is a key determinant of bone resorption in the body [5, [6].

The Immuno-Skeletal Interface

Accumulating data suggests that the immune system and skeletal systems are deeply integrated, forming a nexus referred to as the immuno-skeletal interface (ISI). The ISI exists as a consequence of shared cells and cytokine effectors that play discrete roles in immune and skeletal function. Under normal physiological conditions, the immune system secretes bone protective factors such as OPG [7, [8] which may be lost when the immune system is chronically suppressed (immunosuppression), leading to an accelerated rate of basal bone resorption [9].

HIV infection and the Immuno-Skeletal Interface

Indeed, even before exposure to ART, patients with HIV infection have long been recognized to exhibit low BMD [10] but the cause has remained unclear. Multiple risk factors are recognized to co-exist in HIV-infected populations, including high rates of alcohol consumption and smoking and AIDS-associated pathologies such as low BMI, hypogonadism and kidney disease, that may contribute to bone loss. However, an immunocentric basis for bone loss likely exists in HIV-infected persons. We have performed proof of concept studies in the HIV-transgenic rat, an animal model of HIV infection that lacks many of the confounding influences on bone that are associated with human HIV patients. These studies indeed revealed a significant 75% decline in expression of bone marrow OPG, as a consequence of defective B cell OPG production [11]. This loss of OPG, coupled with a dramatic 5-fold increase in RANKL production by B cells, accounted for a significant increase in osteoclast differentiation. Overall in vivo markers of bone resorption were increased by 43%, while bone formation markers were unchanged. This increase in the rate of bone resorption led to a significant loss of BMD, quantified by dual-energy X-ray absorptiometry (DXA), with a percent change between HIV transgenic rats and control groups of −36% in the Femurs, −29% in the tibias and −21% in the lumbar spine. Because BMD quantifications by DXA reflect integrated measurements of bone we further performed independent trabecular and cortical bone microarchitecture analysis in HIV transgenic rats, which revealed a percent change of −32% in bone volume fraction (BV/TV) between HIV transgenic and control rats. Furthermore, cortical volume was also significantly reduced by −18.7% [11].

We have recently translated the animal studies into a human HIV cohort involving 57 HIV+ individuals and 56 HIV- controls [12]. As expected a significance increase (p=0.007) in serum C-terminal telopeptide of Type I collagen (CTx), a sensitive and selective bone resorption marker, was observed in HIV+ subjects compared to HIV- controls (0.19 (0.15,0.28) vs. (0.31 (0.22,0.38) respectively: Median (95% CI). Elevated bone resorption was associated with a significant (p=0.005) increase in B cell expression of RANKL (HIV+: 16.5 (11.0, 29.0) vs. HIV- 36.0 (20.0, 48.0): Median (95% CI)). Furthermore, B cell

expression of OPG was significantly (p=0.04) decreased (HIV+ 66.0 (60.0, 71.0) vs. HIV- 54.0 (37.0, 62.0): Median (95% CI)). These changes remained significant after multivariable analysis adjusted for the baseline osteoporosis risk factors age, gender, race, BMI, smoking, past 30-day alcohol consumption and fracture history, using multiple linear regression. Interestingly, the B cell RANKL/OPG ratio was found to significantly correlate with total hip (p=0.003) and femoral neck (p=0.008) BMD in HIV+ subjects [12]. Mechanistically, na ve, resting memory and exhausted tissue-like memory B cell subsets were all found to express significantly higher amounts of RANKL (p=0.001, 0.006 and 0.002 respectively) [12]. Taken together with the animal model these findings in humans suggest an underlying immuno-centric disturbance in the ISI that likely accounts for an undercurrent of accelerated HIV-induced bone loss, aligned with B cell dysfunction, in HIV-infected subjects.

Aging and the Skeleton

Declines in sex steroids [1] and development of an inflammatory state, often referred to as “inflammaging” [13] may be key driving forces in age-associated bone loss. However, irrespective of the complex overarching etiology in the context of aging, in terms of the final downstream effectors of osteoclastogenesis an increase in OPG has been documented in aging humans [14, [15] and in mice [16] and may be an essential compensatory mechanism to combat excessive RANKL and osteoclastic bone resorption during aging. Although osteoblast lineage cells are considered an important source of physiological OPG, osteoblast OPG production declines with age, suggesting another source of compensatory OPG during aging. Indeed we have reported that mouse B cells produce increased amounts of OPG in aged animals, implicating B cells as the likely source of elevated OPG [16]. A key issue in the context of HIV infection is whether the compensatory increase in OPG by B cells during aging, may be lost given evidence for diminished production of OPG by B cells (and increased RANKL production) in both animal models and in human subjects. If so, loss of this first line of protection from overproduction of RANKL may lead to an exacerbated bone loss in the context of HIV infection and aging. Studies to quantify the production of OPG (and RANKL) by B cells in aging HIV-infected patients are now ongoing in the WIHS.

In the context of women and menopause, both B cells and T cells have been shown to be key sources of enhanced RANKL production in postmenopausal women relative to premenopausal women and postmenopausal women receiving estrogen replacement [17]. In addition, young women undergoing elective surgical ovariectomy lose a significant amount of BMD (−6% at femoral neck and −4% in the lumbar spine) in the first year, concurrent with a significant increase in activation and TNFα-production by circulating T cells, within 1 months ovariectomy and sustained for at least 3 months (p<0.05) [18]. TNFα is a potent inflammatory cytokine that suppresses OPG and promotes RANKL and is unique in its ability to synergize with RANKL at the level of signal transduction to intensify osteoclastogenesis and resorptive activity [19, [20, [21, [22].

ART and bone loss

Although it is clear that HIV-infection is a risk factor for low BMD, ART has long been associated with bone loss independently of HIV-induced bone loss. This paradoxical

discovery has an uncertain etiology and in vitro and animal studies have not effectively modeled the effects of ART in vivo in the context of humans with HIV infection. Although, certain ART-containing regimens, particularly those containing tenofovir appear to generate exacerbated bone loss, it is now clear that in general most bone loss is independent of antiretroviral regimen [23], suggesting a common mechanism. One such mechanism recently studied is immune reconstitution. Repopulation of immune cells and regeneration, in part of the immune system, is a common event associated with all classes of ART. Using an animal proof of concept we recently demonstrated that repopulation of T cells in the context of an immunodeficient animal model leads to an inflammatory response and immune reactivation characterized by T cell, B cell and monocyte production of RANKL and/or TNFα that drives up bone resorption and induces significant bone resorption and structural damage [24]. Importantly, data suggest that this inflammatory bone loss is of short duration, predominantly in the first 6 to 12 months after ART-initiation [25], suggesting a window of opportunity for anti-osteoporotic intervention. In response we recently performed a phase IIb, double-blind, placebo-controlled trial, 63 non-osteoporotic ART-naïve male and female HIV-patients initiating ART with atazanavir/ritonavir+tenofovir/emtricitabine. Subjectes were randomized to a single administration of placebo or the antiosteoporotic agent zoledronic acid (5mg). Zoledronic acid caused a 65% reduction in bone resorption (CTx) relative to the placebo arm at 24 weeks (0.117 ng/ml vs. 0.338 ng/ml, $p<0.001$) and completely blocked BMD loss [26]. These data suggest that ART induced bone loss can be prevented by a single administration of zoledronic acid at time of ART-initiation. Due to potential rare but serious side-effects of anti-osteoporotic agents, their long term use is now being discouraged, and even a single administration will require additional studies to prove efficacy and safety.

More research is now needed to establish the skeletal profile and rate of bone turnover during aging and in the context of menopause in HIV-infected women. To this end recent studies in the WIHS have begun to address this important issue.

Osteoporosis and low bone mineral density (BMD) in HIV-infected WIHS women

The first study of BMD in the WIHS cohort, a cross-sectional analysis of lumbar spine (LS) and femoral neck (FN) BMD among 274 HIV-infected and 152 uninfected women, found that HIV-infected women had lower BMD than uninfected women [27]. In multivariate analyses, the odds of having osteopenia (T score <-1.0) were significantly greater in both HIV-infected HAART naïve women (OR 4.36, 95%CI: 1.61, 11.8) and HIV-infected women receiving protease inhibitor-based HAART (OR 3.72, 95%CI: 1.43, 9.68) compared with HIV-uninfected women, while HAART regimens that did not contain protease inhibitors were not significantly associated with BMD [27]. These findings were consistent with several other cross-sectional studies published at the time which also reported low BMD in HIV-infected women [28, [29, [30, [31, [32]. Subsequently, a longitudinal study of 100 HIV-infected and 68 HIV-uninfected premenopausal women in WIHS found that while BMD was initially lower in HIV-infected women (mean age 40 years) compared with uninfected women (mean age 36 years), stable BMD or relatively small amounts of bone loss was

observed with over 2.5 years of follow up, and bone loss was not associated with antiretroviral therapy among HIV-infected women [33]. In that study, the annual percent decrease in LS and FN BMD was similar between HIV-infected and uninfected women, with a mean decrease of approximately 0.4–0.8% per year, and the relationship between bone loss and HIV status were further attenuated after adjusting for age, weight, and index BMD [33]. In contrast, in a separate cohort of postmenopausal women with a mean age of 57 years, annualized rate of bone loss was 2–3 times greater in HIV-infected than uninfected women at the spine and radius and bone turnover markers were higher in HIV-infected women [34]. In multivariate analyses, HIV status predicted bone loss at the spine, radius and hip. In a subset of postmenopausal women with high resolution peripheral quantitative CT (HRpQCT) imaging of the radius and tibia in additional to DXA evaluations, cortical area and thickness of the tibia were found to be 11–12% lower in HIV-infected than uninfected women [35]. Taken together, these data suggest that systemic bone loss due to HIV-associated immune activation is accelerated by estrogen deficiency after the menopausal transition.

Relationship between Adiposity and Bone Mineral Density

The WIHS metabolic substudy, a longitudinal study of 318 HIV-infected and 122 uninfected women, examined how body composition changes including lean mass and regional body fat affected BMD over 5 years of follow-up [36]. In this substudy, HIV-infected women were older and more likely to be postmenopausal (26% vs 3%) than uninfected women. HIV-infected women also had lower body mass index (BMI), and lower trunk, leg and total body fat than HIV-uninfected women, however body composition measures such as trunk fat, leg fat, fat free mass (FFM), total body fat (TBF), and percent body fat (PBF) were stable or increasing over time for both HIV-infected and HIV-uninfected women. After adjustment for demographic and clinical factors, HIV-infection was associated with decreased BMD at the total hip (TH), FN, and LS. Moreover, greater lean mass (FFM) was independently associated with increased BMD at all three sites, and greater total fat was associated with increased TH and FN BMD. When replacing total fat with trunk fat and leg fat in the model, greater trunk fat was associated with increased TH and FN BMD, whereas leg fat was not, suggesting that weight bearing fat may be a more important predictor of BMD in the hip, regardless of HIV status [36].

Additional analyses of the WIHS Metabolic Study evaluated the relationship of the adipocyte-derived hormones (adipokines) adiponectin and leptin with BMD in HIV-infected and uninfected women [37]. HIV-infected women had higher adiponectin (median 6.2μg/mL vs. 5.6μg/mL,) and lower leptin (11.7ng/mL vs. 19.8ng/mL) levels at baseline compared with HIV-uninfected women. HIV-infection was associated with lower BMD at the LS, FN, and TH in multivariable models, with little change in the association of HIV with lower BMD at each site after additional adjustment for adiponectin or leptin. Among HIV-infected women, higher adiponectin was associated with lower TH BMD, whereas higher leptin was associated with higher BMD at FN and TH, however after multivariable adjustment, adipokines showed little association with BMD at any site, suggesting that alterations in serum adiponectin and leptin do not explain low BMD in HIV-infected women [37].

Fractures in HIV-Infected Women

We previously reported that among 1728 HIV-infected and 663 uninfected WIHS participants, who were predominantly premenopausal, 5-year fracture incidence was similar between HIV-infected women in unadjusted analyses (1.8/100 vs. 1.4/100 person years (py), p=0.10) as well as in multivariate models [38]. Factors associated with fracture incidence in multivariate models included traditional risk factors such as older age, white race (vs. African American), hepatitis C virus (HCV) infection, prior fracture history and elevated serum creatinine level. Among the subset of HIV-infected women, older age, white race, current cigarette use, and history of AIDS defining illness were associated with fracture incidence.

With 5 additional years of follow-up, we subsequently found that as the WIHS cohort aged, fracture rates increased, with fractures at any site observed in twice as many women compared to our previous study (17.5% vs. 8.6%) [39]. Fracture rates particularly increased among the HIV-infected women, who had higher 10-year fracture incidence when compared to HIV-uninfected women (2.19/100py vs. 1.54/100py, p=0.002); these differences in fracture incidence in HIV-infected compared with uninfected women remained statistically significant in multivariate models, (adjusted Hazard Ratio 1.32, 95% CI: 1.04, 1.69). In multivariate models, HIV status, older age, white (vs. black) race, prior fracture, history of cocaine use, and history of injection drug use were significant predictors of incident fracture, although unlike our prior study, renal insufficiency and HCV infection were not significantly associated with fracture. Among the subset of HIV-infected women, age, white race, cigarette smoking, prior fracture history, and history of AIDS defining illness were associated with increased fracture incidence [39].

Falls in HIV-infected Women

Fracture is almost always precipitated by a fall and fragility fracture by a fall from standing height or less. Neurological damage is another well studied complication of chronic HIV infection/ART and along with increased general frailty may lead to an increased propensity to falls in HIV populations.

In a cross-sectional study of 1,412 HIV-infected and 650 HIV- uninfected women in the WIHS with mean age 48 years, we determined the frequency of any self-reported fall and multiple (≥2) falls occurring in the prior 6 months, and determined risk factors associated with falls [40]. We found a high prevalence of falls in the WIHS cohort, with at least one fall reported in 263 HIV-infected (19%) vs. 119 HIV-uninfected (18%) women, and ≥2 falls reported in 133 HIV-infected (9%) vs. 65 HIV-uninfected (10%) women. There was no difference in the number of falls reported by HIV-infected compared with uninfected women in either bivariate or multivariate analyses. Factors associated with report of any fall included traditional fall risk factors, such as older age, current or past marijuana use, depressive symptoms as measured by the Center for Epidemiology Studies Depression scale, obesity (body mass index ≥30kg/m^2), peripheral neuropathy (self-report of numbness, tingling, or burning sensations in arms, legs, hands or feet lasting for ≥2weeks); subjective cognitive complaints, and number of number of central nervous system (CNS) active

medications used (i.e. anticonvulsants, antidepressants, antipsychotics, benzodiazepines/sedatives, and muscle relaxants). Factors associated with multiple (compared with single) falls included current crack, cocaine or heroin use, subjective cognitive complaints, and neuropathy. HIV-disease or treatment-specific factors including measures of HIV disease severity (CD4 nadir, prior AIDS), current HIV disease control (current CD4+ count, suppressed HIV RNA viral load, or current antiretroviral use), or HIV-treatment related factors (including current ART use, as well as current and prior use of didanosine, stavudine, zidovudine, or efavirenz) were not associated with either any fall or with multiple falls in multivariate analyses. Overall, the occurrence of self-reported falls was similar in HIV-infected and HIV-uninfected women with a mean age of 48, and HIV-disease or treatment related characteristics were not associated with fall risk among those with HIV infection. Factors associated with cognition, such as subjective cognitive complaints, depressive symptoms, and use of CNS active medications, as well as substance use were identified as risk factors for falls, and could be important areas to target in falls prevention efforts as HIV-infected women age. Given the prevalence of low BMD as well as observed fracture incidence in HIV-infected women, longitudinal studies are needed to determine whether the incidence and consequence of falls will be greater in HIV-infected than uninfected women as they age.

Conclusion

In conclusion, although loss of BMD among HIV-infected subjects, and associated with ART has long been recognized, it is only relatively recently that the repercussions of this bone loss in terms of fracture incidence have become apparent. With numerous large population based studies all reporting significant elevations in fracture incidence within HIV-infected subjects, combined with a rapid aging of the HIV demographic to an age group where fracture becomes significantly more frequent, concerns over an epidemic of bone fractures in the future is mounting. Postmenopausal osteoporosis is the archetypal osteoporotic condition and a putative clash between menopause- and HIV/ART-induced bone loss is worrisome. Recent studies in the WIHS suggest a significant increase in fracture prevalence has begun to emerge and is significantly associated with older age. Coupled with a high incidence of falls in WIHS women, mechanisms to prevent fracture will be urgently needed in the foreseeable future. Recognition and acceptance of the problem is first necessary before preventative strategies can be devised and implemented. Ongoing research within the WIHS is actively attempting to collect this information and the WIHS is likely to be instrumental in defining the future standard of care to protect the gains in health afforded by ART by protecting skeletal longevity.

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