

A PEER-REVIEWED ARTICLE

Update: Bone mineral density loss is common complication in HIV infection

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Effective antiretroviral therapy (ART) has led to increased longevity in HIV-infected individuals which in turn has led to the recognition of a number of metabolic abnormalities in this population including insulin resistance and diabetes, dyslipidemia, lipoatrophy and lipohypertrophy, and bone disease. Bone mineral density (BMD) loss with resultant osteopenia and osteoporosis has emerged as one of the most common metabolic complications in HIV-infected patients in the modern treatment era. There is concern that as HIV-infected patients continue to age, there may be a dramatic rise in the incidence of fragility fractures and their considerable morbidity and mortality in this population. While no prospective trials on fracture prevalence have been published, a retrospective study comparing fractures in 8,525 HIV-infected and 2,208,792 HIV-uninfected patients found an increased prevalence in those with HIV (2.9 versus 1.9 per 100 patient years, $p < 0.0001$).¹

Prevalence

Several older and relatively small studies have reported increased prevalence of low BMD with osteopenia and osteoporosis in HIV-infected subjects.^{2,3,4,5,6} More recently three large trials and a careful meta-analysis of previous studies looking at the issue of BMD loss in HIV-infected patients have been published. A meta-analysis of eleven cross-sectional studies that examined the prevalence of reduced BMD in 884 HIV-infected patients and 654 HIV-uninfected controls found that 67% of the HIV-infected patients had reduced BMD and 15% had osteoporosis. The HIV-infected patients demonstrated a 6.4-fold increased risk of osteopenia and a 3.7-fold increased risk of osteoporosis compared to HIV-uninfected controls.⁷

A cross-sectional survey of 492 mostly male HIV-infected subjects with a median age of 43 from the French Aquitaine cohort (a prospective hospital-based cohort of HIV-infected individuals under routine clinical management in southwestern France initiated in 1987) reported that 54.6% of men and 51.1% of women met WHO criteria for osteopenia. Osteoporosis was found in 33.7% of men and 8.3% of women.⁸

In an analysis of BMD in 559 older men (median age 55) with HIV or at risk for HIV from the Cohort of HIV at-risk Aging Men's Prospective Study (CHAMPS), BMD was found to be significantly lower in the HIV-infected group compared to those without HIV infection.⁹ Data from the large Gilead Study 903, involving 600 antiretroviral-naïve patients with a mean age of 36 who were randomized to receive either tenofovir/lamivudine/efavirenz or stavudine/lamivudine/efavirenz, showed a baseline prevalence of osteopenia of 23% in the tenofovir group and 28% in the stavudine group, significantly higher than the prevalence among US adults in the general population.¹⁰

Risk factors

The risk factors for osteopenia/osteoporosis among HIV-infected patients can be divided into two categories: traditional or established risk factors and HIV-specific risk factors. Some of the more common established risk factors are summarized in Table I. HIV-specific risk factors are less well-defined but there are data to suggest that HIV infection itself and the duration and severity of infection contribute to low BMD. The effect of antiretroviral therapy will be discussed separately.

Due to lifestyle, physiologic and psychologic factors, HIV-infected patients are very likely to have many of the established risk factors for low BMD, such as smoking, heavy alcohol use, physical inactivity, low body weight, oligo/amenorrhea, male hypogonadism (including that associated with opiate use), depression, and nutritional deficiencies including inadequate calcium intake and vitamin D insufficiency. Therefore, the increased prevalence of BMD loss among HIV-infected patients is likely due to the combined influence of established and HIV-specific risk factors.

In the Aquitaine cohort study cited above, low CD4 count nadir was identified as an independent risk factor for low BMD among women. In both men and women, older age was also an independent risk factor for BMD loss.⁸ Whether or not older age correlated with longer duration of HIV infection was not addressed in their analysis. The findings from the CHAMPS study are probably more revealing since the HIV-infected and HIV-uninfected men in this cohort were very well matched with regards to established risk factors for low BMD. In the cohort as a whole, HIV infection was found to be independently associated with low BMD along with non-black race, lower body weight, and low testosterone. Among the HIV-infected men, longer duration of HIV infection was associated with lower BMD of the lumbar spine.⁹

In the Gilead Study 903 that showed a high prevalence of baseline osteopenia in 600 antiretroviral-naïve patients, lower baseline BMD at the lumbar spine was associated with lower weight, increased age, and male sex.¹⁰ Taken together these data suggest that HIV infection itself, as well as the duration and severity of infection as indicated by CD4 count nadir, may predict low BMD. More and better designed studies are needed to clearly identify HIV-specific risk factors for BMD loss.

Effect of ART

Several older cross-sectional studies have reported increased BMD loss in patients receiving ART, in particular protease inhibitor (PI)-based therapy. In the meta-analysis by Brown and Qaqish, antiretroviral treated patients (n = 824) had a 2.5-fold increased risk of osteoporosis compared to antiretroviral-naïve patients (n = 202). Patients treated with PI-based therapy (n = 791) had a 1.6-fold increased risk of osteoporosis compared to non-PI treated patients (n = 410).⁷ However, in the former analysis none of the studies adjusted for other potentially contributing factors such as age or duration and severity of HIV infection. In the latter analysis, few studies adjusted for important confounding factors such as age, duration and severity of HIV infection, and length of antiretroviral treatment.

The best way to assess the effect of ART on BMD loss is by using a longitudinal study design that looks at the effect of ART over time and avoids the inherent bias of cross-

sectional studies. In four studies that followed BMD in ART-experienced patients (n = 228), BMD either increased or was stable during the study interval (48 to 72 weeks). No significant difference was seen in BMD in those patients on PI-based ART.^{7, 11} In two switch trials involving 80 patients who changed from PI-based therapy to nonnucleoside-based or nucleoside-sparing regimens, no significant difference in BMD was detected between groups.⁶ In contrast, in two studies that followed BMD over time in patients initiating ART, one of which was the large Gilead Study 903, initiation of ART was associated with decreased BMD from baseline. These studies followed a total of 642 patients over a period of 144 weeks. The Gilead trial identified a significantly greater decline in BMD in the lumbar spine in patients on tenofovir compared to those on stavudine (-2.2% vs -1.0%).^{7, 10} Overall the data from these longitudinal trials suggest that there is initial moderate BMD loss after initiation of ART which then stabilizes or improves over time. PI use was not implicated in excess BMD loss in these studies. The clinical significance for the use of tenofovir based on these data remains unknown at this time, although there is concern that tenofovir use in children and adolescents could preclude development of adequate peak bone mass. Trials in children are ongoing to better assess the effect of tenofovir on BMD in this age group.

Pathogenesis

Because the etiology of BMD loss in HIV-infected patients is likely multi-factorial, trying to determine the pathogenesis of decreased BMD in HIV infection is complex. However, a number of studies have looked at different aspects of this issue and provide some insight. Two pre-HAART studies using information from bone biopsies and/or measurement of biochemical markers of bone formation and resorption found decreased bone formation with decreased level of osteocalcin, a bone formation marker, that correlated with CD4 count.^{12, 13} One of the studies involving 50 female patients with a mean age of 37 found dysregulation of bone metabolism with increased resorption and decreased formation, as well as vitamin D deficiency.¹³ Another study that looked at bone metabolism biomarkers in 16 patients before and after starting HAART out to 24 weeks also reported uncoupling of bone formation and resorption at baseline. Interestingly, there was significant re-synchronization of bone metabolism after initiation of HAART.¹⁴ In another longitudinal study of 93 HIV patients on HAART followed over 72 weeks, the authors found high levels of markers of both bone formation and resorption over the course of the study with a modest increase in BMD over time.¹⁵

Vitamin D deficiency is common in the general population and is associated with osteoporosis. Several studies have reported high rates of vitamin D deficiency in HIV patients ranging from 23 to 92%. A recent study that measured vitamin D levels in 54 HIV-infected patients in an ambulatory clinic found that 36.8% had moderate and 10.5% severe vitamin D deficiency. Severe vitamin D deficiency tended to be associated with lactose intolerance.¹⁶

Chronic inflammation in HIV infection leading to cytokine activation has also been proposed as a possible mechanism for increased bone resorption. Advanced HIV infection is associated with TNF activation which in turn activates and upregulates other pathways that lead to osteoclast differentiation and bone resorption.¹⁷ In vitro, HIV-1 has been shown to cause apoptosis of primary osteoblasts through TNF activation.¹⁸

Prevention and management

There are no current formal recommendations to screen HIV patients for osteopenia or osteoporosis with DEXA studies. Given the high prevalence of BMD loss in patients with HIV infection, there may be such recommendations in the future. The National Osteoporosis Foundation guidelines recommend DEXA screening for postmenopausal women over age 65. They also recommend that all postmenopausal women and men over 50 be clinically evaluated for additional risk factors. In HIV-infected patients it may be prudent to consider DEXA screening in those with multiple risk factors such as low BMI, smoking, menopause or hypogonadism, steroid exposure, or history of previous fragility fracture. Preventative strategies are appropriate for all HIV-infected patients including smoking cessation counseling and aids, encouraging regular weight-bearing exercise such as walking or jogging, dietary counseling to promote adequate nutrition and calcium and vitamin D intake and supplementation (calcium 1000-1500 mg/day and vitamin D 400-800 mg/day). Screening for hypogonadism in men and treatment with testosterone should also be considered.

General treatment options for osteoporosis include bisphosphonates, calcitonin, recombinant human parathyroid hormone, hormone replacement therapy, and selective estrogen receptor modulators such as raloxifene. To date, only bisphosphonates have been studied in HIV patients. Several studies have evaluated alendronate in HIV-infected patients with BMD loss and found it to be safe and effective. In the largest of these trials, ACTG study 5163, 80 patients were enrolled in a prospective, randomized, placebo-controlled study to receive once weekly alendronate plus calcium and vitamin D or calcium and vitamin D alone over 48 weeks. The alendronate arm had significant improvements in BMD at the lumbar spine and total hip but not at the femoral neck. No significant adverse events were seen with alendronate treatment. Importantly, in the calcium/vitamin D alone group there were trends towards significant increases in BMD at the lumbar spine, total hip and femoral neck.¹⁹

Summary

Decreased BMD is highly prevalent among HIV-infected patients. The etiology of BMD loss in this population is multi-factorial and appears to be due to the high frequency of established risk factors and HIV infection itself. The mechanisms by which HIV infection contribute to BMD decline need further study. HAART appears to actually stabilize BMD loss over time, although individual agents such as tenofovir are associated with a larger initial decrease in BMD. Particular attention should be directed to modifiable risk factors such as smoking, physical inactivity, and adequate calcium and vitamin D intake. Screening and treatment should be undertaken according to existing general guidelines and be considered in those with multiple risk factors.❖

Definitions

BMD is measured by dual-energy X-ray absorptiometry or DEXA scan at the femoral head and lumbar spine. The World Health Organization (WHO) defines normal BMD as within 1 standard deviation (SD) of the mean BMD at the time of peak bone mass in 30-year-old persons adjusting for race and sex. Low BMD or osteopenia is between 1.0 and 2.5 SD below the mean young adult normal (or T-score between -1.0 and -2.5). Osteoporosis is defined as 2.5 SD or more below the mean young adult norm (or T-score < -2.5).

Table 1. Common Established Risk Factors for Low BMD

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| Smoking |
| Alcohol (≥ 3 drinks/day) |
| Low BMI |
| White race |
| Postmenopausal status in women |
| Inadequate physical activity |
| Increased age |
| Steroid exposure |
| Low calcium intake |
| Vitamin D deficiency |

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