Emerging Bone Problems in Patients Infected with Human Immunodeficiency Virus

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Recently, a high incidence of osteopenia and osteoporosis has been observed in individuals infected with human immunodeficiency virus (HIV). This problem appears to be more frequent in patients receiving potent antiretroviral therapy. Other bone-related complications in HIV-infected individuals, including avascular necrosis of the hip and compression fracture of the lumbar spine, have also been reported. People living with HIV have significant alterations in bone metabolism, regardless of whether they are receiving potent antiretroviral therapy. The underlying mechanisms to account for these observations remain unknown, although studies are underway to examine the relationship between the bone abnormalities and other complications associated with HIV and antiretroviral therapy. HIV-infected patients with osteopenia or osteoporosis should be treated similarly to HIV-seronegative patients with appropriate use of nutritional supplements (calcium and vitamin D) and exercise. Hormone replacement and antiresorptive therapies might be also indicated.

The introduction of highly active antiretroviral therapy (HAART) with the use of protease inhibitors (PIs) has resulted in significant reductions in morbidity and mortality from HIV infection in recent years [1, 2]. Although initial strong enthusiasm for HAART led to its widespread use early in HIV infection, practitioners have now become more cautious in early initiation of HAART in light of reports concerning serious and potentially irreversible toxicities associated with numerous antiretroviral drugs [3–10]. These toxicities include the development of diabetes mellitus, insulin resistance, hyperlipidemia, lipodystrophy, and lactic acidosis [4–9].

Recently, a high incidence of osteopenia and osteoporosis has been observed in HIV-infected individuals. This problem seems to be more frequent in patients receiving potent antiretroviral therapy, although a specific contribution (if any) of the drugs used in combination regimens has yet to be established [11–14]. Our group, in a cross-sectional study, observed a significantly higher incidence of osteopenia and osteoporosis in individuals receiving combination therapy that included nucleoside analogs and PIs compared with both HIV-infected individuals not receiving PIs and seronegative individuals [12]. This study needs further confirmation. There have been several reports of other bone-related complications in HIV-infected individuals, including avascular necrosis of the hip and compression fracture of the lumbar spine [11, 15–20]. Clearly, people living with HIV have significant alterations in bone metabolism, regardless of whether they are receiving potent antiretroviral therapy. The underlying mechanisms to account for these observed effects remain unknown, although studies are underway to examine the relationship between the bone abnormalities and other complications associated with HIV and antiretroviral therapy.

OSTEOPOROSIS

Worldwide, osteoporosis is a significant cause of morbidity and mortality, with an estimated 10 million people in the United States already living with this disease [21]. It is a skeletal disorder characterized by compromised bone strength predisposing to an increased risk...
of fracture. Bone strength refers to a combination of bone quantity and quality. Bone quantity is measured by means of bone mineral density (BMD), a commonly used surrogate marker for bone strength. In a consensus statement from 1994, the World Health Organization (WHO) agreed to standard definitions of osteoporosis according to normalized measurements of BMD. By WHO criteria, a $t$ score is defined as the number of SDs above or below the average BMD for race- and sex-adjusted population norms determined at peak bone mass (which occurs at $\sim$30 years of age). A $z$ score compares the patient to population norms adjusted for age, race, and sex. Currently, WHO defines osteoporosis as a $t$ score $\leq -2.5$ SDs. Osteopenia is defined as a BMD between $-1$ and $-2.5$ SDs. Osteoporosis without a history of fracture carries a 4–5-fold increase in fracture risk compared with individuals with normal BMD. A history of fracture and diagnosis of osteoporosis carries a 20-fold increased risk, and osteopenia alone carries a 2-fold increase in fracture risk [22–24].

Gradual bone loss is a common occurrence with aging and is often referred to as primary osteoporosis. Men and women naturally begin to lose bone around the age of 35 years, at a rate of 0.5%–1% per year. Women also lose bone at an accelerated rate after menopause. In addition to female sex and age, additional risk factors include white race, low weight, smoking, excessive alcohol use, and history of fracture. A number of secondary causes of osteoporosis are also well known, including corticosteroid use, hypogonadism, hyperthyroidism, prolonged immobility, nutritional deficiencies or malabsorption, chronic illness, and concurrent medications such as anticonvulsants or anticoagulants. All of these potential confounding factors must be accounted for in studying the relationships between bone abnormalities, HIV, and antiretroviral therapies.

**BONE METABOLISM IN HIV-INFECTED INDIVIDUALS**

Before the era of HAART, studies indicated that bone mineral metabolism was only minimally affected in HIV-infected individuals. In one study, Paton et al. [25] reported that 45 HIV-infected patients had marginally lower BMD at the lumbar spine than HIV-seronegative controls ($P = .04$). The subjects and controls did not differ in total body or hip BMD. At longitudinal follow-up (15 months), a small decrease in total body BMD ($-1.6\%; P = .02$) was observed, but there was no significant reduction in spine and hip BMD. We conducted a similar cross-sectional analysis in 20 HIV-infected subjects naive to antiretroviral therapy to evaluate whether osteopenia was a manifestation of HIV infection itself. Total body, hip, and spine BMD were measured by dual X-ray absorptiometry (DXA), with no significant differences from the general population. There was also no significant correlation between CD4 count, HIV virus load, and BMD among our cohort. Most recently, at the 2001 Conference on Retroviruses and Opportunistic Infections, additional studies were presented that showed a significant prevalence of low BMD in HAART-naive patients compared with the general population [26–28]. In the larger of these studies, the prevalence of osteopenia/osteoporosis was 28%, compared with the 16% that one would expect in the general population. These studies suggest that HIV infection itself has a significant impact on bone metabolism and may be a contributing factor in the pathogenesis of reduced BMD.

Other studies have examined biochemical markers of bone metabolism and bone biopsy specimens of therapy-naive HIV-infected individuals in comparison with healthy seronegative controls. The most characteristic finding was a marked decrease in the concentration of osteocalcin (a marker of bone formation) and an increase in C-telopeptide (a marker of bone resorption) that correlated with enhanced activation of the tumor necrosis factor system and increasing severity of HIV disease [29–31]. Because numerous cytokines are known to induce differentiation of bone marrow precursors into osteoclasts that would favor bone resorption and the development of osteoporosis, it seems that immune system activation could play a role in the development of bone abnormalities associated with HIV.

To date, the only published study of assessments of bone samples from antiretroviral therapy–naive HIV-infected subjects did not show alterations in BMD or biochemical differences in bone metabolism compared with healthy controls, except for decreased levels of osteocalcin in individuals with lower CD4 counts [32]. The number of osteoclasts was found to be significantly lower in HIV-infected individuals rather than higher, as previously predicted. These findings suggest that progression of HIV may promote a decline in activity of bone metabolism and that the low-BMD “phenotype” observed in treated individuals is unlikely to be the result of HIV disease alone. The strength of this conclusion is limited because of the cross-sectional nature of the studies. Larger prospective studies are currently underway to test and answer some of these questions.

**BONE IN HIV-INFECTED PATIENTS RECEIVING ANTIRETROVIRAL THERAPY**

As part of our ongoing studies of metabolic complications associated with HAART, we performed a cross-sectional analysis of whole-body, lumbar spine (L1–L4), and proximal femur BMD in 112 male subjects (HIV-infected patients receiving HAART that included a PI, HIV-infected patients not receiving a PI, and healthy HIV-seronegative adults) using DXA scans [12]. The median exposure to PIs in the group receiving PIs...
was 104 weeks. Men receiving PIs had lower median t scores for the lumbar spine BMD compared with the other 2 groups. On the basis of lumbar spine BMD t scores, 50% of the subjects on PIs were classified as osteopenic or osteoporotic according to the WHO classification. The relative risk for osteoporosis in these subjects was 2.19 (95% CI, 1.13–4.23) when compared with HIV-infected subjects not receiving PIs. Subjects with more prolonged use of PIs tended to have more negative t scores in the lumbar spine (Pearson correlation coefficient = −0.19, P = .14), but this correlation did not reach statistical significance.

We also performed an assessment of bone metabolism in a different cohort of 73 HIV-infected subjects receiving therapy with 2 nucleosides and a PI [33]. Ninety-five percent of the cohort had an undetectable virus load, and the median CD4 cell count was >540 cells/mm³, thus representing a group that had responded remarkably well to HAART. Forty-three percent of the subjects were osteopenic/osteoporotic according to the WHO definition. There was no association of osteopenia with regard to specific PIs. A significant proportion of subjects had both increased markers of bone resorption and bone formation, including elevations in urine pyridinolines, bone alkaline phosphatase, and osteocalcin. This is in sharp contrast with the previous observations of low osteocalcin levels in subjects with advanced disease. The levels of bone alkaline phosphatase and pyridinolines in urine correlated with BMD. Testosterone and thyroid-stimulating hormone levels were normal in this population, and they did not correlate with BMD, either in the lumbar spine or in the hip. More than 50% of the patients had urinary calcium levels ≥ 200 mg/24 h, and 25% had > 300 mg/24 h. Another more recent study looking at similar bone metabolic parameters in HIV-infected children also found HAART-associated losses in BMD that were associated with an increased rate of bone turnover [34].

Other studies have shown a more accelerated loss of BMD in individuals receiving potent antiretroviral therapy, but the association with PI use remains speculative [13–14]. Most patients have also received nucleoside analog reverse transcriptase inhibitors (NRTIs) at the time of PI therapy. The use of NRTIs has been associated with mitochondrial toxicity and lactic acidosis. Preliminary data have been presented correlating osteopenia/osteoporosis, total duration of NRTI therapy, and magnitude of NRTI-related lactic acidemia [35].

Unfortunately, given the cross-sectional nature of these recent studies, it is impossible to attribute cause and effect and to measure the cumulative effects of other important but common risk factors for BMD loss in HIV-infected individuals. These include history of wasting or poor nutrition, past steroid usage (i.e., for pneumocystis carinii pneumonia or myopathy), hormonal deficiencies, or the potential contribution of HIV-related immune system activation and immune reconstitution. Additional prospective, longitudinal studies are necessary to determine the exact role of each of these factors in the pathogenesis of HIV-related bone mineral loss.

**ASSESSMENT AND RECOMMENDATIONS**

Current diagnosis and treatment of osteopenia/osteoporosis in HIV-infected individuals is primarily based on recommendations used for management of disease in HIV-seronegative adults. Measurement of BMD as a routine test in HIV-infected patients is not recommended. Rather, a detailed history and physical examination to assess an individual’s fracture risk is advised, in addition to an evaluation of nutritional status and potential secondary causes of osteoporosis. Abnormal laboratory values obtained during the course of HIV treatment (i.e., elevated alkaline phosphatase or low testosterone) should also prompt consideration of further testing for osteoporosis [36].

As noted above, the primary diagnoses of osteopenia or osteoporosis are based on the WHO definitions according to measurements of BMD. The most widely used technique for determining BMD is DXA. DXA scanning measures bone mass and density in central regions of interest (hip and spine) as well as appendicular regions (wrist, forearm, heel). It has become the gold standard to which all other bone densitometry technologies are compared [37–39]. DXA studies are also useful to define fracture risk as well as to measure the effectiveness of various therapies on bone mass [21]. Biochemical markers of bone turnover can provide complementary information to DXA scans, including changes in bone remodeling that can be identified before changes in BMD [21]. However, the use of such markers in predicting future changes in bone mass and fracture risk remains controversial.

Until studies are completed that specifically address the treatment of low BMD in HIV-infected patients, it seems reasonable to pursue osteoporosis treatment strategies that have been proven effective in the general population. A careful search for reversible causes of secondary osteoporosis should be performed, and vitamin D and calcium intake should be optimized to meet recommended dietary levels. For calcium, the recommended intake from all sources is 1500 mg/d, and for vitamin D, the recommended intake is 400–1000 IU/d. These recommendations have been in place for years, but only ~50% of American adults meet them. Other nutrients are also important in relation to bone health. Diets with very high protein content, excess caffeine, phosphorus, and sodium can increase calcium losses, but their contribution does not appear to be very important if the individual has an adequate intake of calcium. Moderate physical activity is also recommended to help preserve bone mass.

For more severe cases, the use of hormone replacement therapy (if otherwise indicated), bisphosphonates, calcitonin, or...
raloxifene is recommended [21]. These agents have not been tested specifically in HIV-infected individuals, but there are no good biological reasons to think that these treatments would fail. Although all of these agents have shown efficacy with BMD as the primary outcome, only the bisphosphonates have consistently shown strong efficacy in reducing the risk of vertebral and nonvertebral fractures [21]. These agents typically reduce the risk of vertebral fractures by 30%–50%. No significant interactions are expected with PIs or other antiretroviral therapies (J. Gerber, personal communication), although no studies have been conducted yet.

**OSTEONECROSIS**

Another emerging bone-related problem in HIV-infected individuals is osteonecrosis, a relatively rare occurrence that is usually the result of lack of an adequate arterial blood supply to the bone. The femoral head is most commonly affected, and patients usually present with pain. However, osteonecrosis in HIV-infected patients has often involved multiple sites [19, 39]. The pathogenesis of this condition is not well known, but factors associated with osteonecrosis have included prolonged steroid use, chronic alcoholism or injection drug use, hypertriglyceridemia, antiphospholipid antibodies, sickle-cell anemia, and radiation exposure. These known risk factors have resulted in postulated mechanisms for the increased frequency of osteonecrosis observed in HIV-infected individuals, including PI-related hypertriglyceridemia, fat redistribution, and increased antiphospholipid production due to enhanced humoral immunity.

A few case reports and one small study suggested that osteonecrosis might be related to HAART [11, 39, 40]. However, there are several reports of this complication before the era of antiretroviral therapy, and in a recent review of 33 cases of osteonecrosis, HIV was found to be the only risk factor in 33% of the cases [39]. Osteonecrosis was more common (55%) in patients with advanced AIDS, but a significant proportion also had suppressed HIV virus loads and relatively high CD4 counts. In the largest series by Judy Fallon and Henry Masur at the National Institute of Health, 339 asymptomatic patients were followed, along with 118 HIV-negative age and sex-matched controls [20]. They found 15 cases of avascular necrosis of the hip in the HIV-positive patients and none in the controls (P = .015). Factors that did not seem to be associated with avascular necrosis were CD4 cell count, HIV RNA level, or use of a PI. Factors that did seem to be associated with this complication included previous corticosteroid use, lipid-lowering drugs, use of testosterone, and body building/weight lifting.

Medical therapy for osteonecrosis is generally ineffective, and surgery is usually needed. Some asymptomatic patients might not need specific interventions until symptoms appear, as was the case in several patients from the National Institutes of Health cohort. Changing antiretroviral therapy to a non-PI–containing regimen does not appear to help, but treating concomitant predisposing conditions that might cause further osteonecrosis seems to be a reasonable approach.

Clearly, long-term prospective studies are needed to further evaluate the effects of antiretroviral therapies, immune reconstitution, and duration of HIV infection on bone metabolism. Further in vitro and in vivo studies can also provide additional information about the specific effects on bone of both individual and various combinations of antiretroviral drugs. Preliminary studies reveal that different PIs have different effects on bone metabolism, vitamin D metabolism, and the differentiation and function of osteoblasts and osteoclasts [41, 42].

In the meantime, HIV-infected patients with low BMD should be treated similarly to seronegative patients with the appropriate use of nutritional supplements, exercise, hormone replacement, and antiresorptive therapies. Data are lacking with regard to the effects on bone of switching or discontinuing antiretroviral medications, but these approaches may also be reasonable in patients with relatively high CD4 counts or with additional metabolic complications on their current antiretroviral regimens.

**References**


