Livia Tampellini; Carlo Biagetti; Paolo D'Aquino; Marco Borderi; Francesco Chiodo

HIV-HAART and Bone metabolism: prevalence of the osteopenia and osteoporosis among the HIV population

M.D. PhD Livia Tampellini
U.O. Malattie Infettive Bologna
Via Massarenti 9, 40138 Bologna (BO) Italia
Tel.: +39 051 6363355 - Fax: +39 051 6363802 - E-mail: t.livius@libero.it
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ABSTRACT

Since the 1990s many papers have reported on bone metabolism changes even in the pre-HAART era and there has always been a suspicion that the virus was the underlying problem. After the advent of HAART the issue became more complicated because on the one hand HIV-infected patients can live longer but on the other they present the side-effects of treatment and older age. We will review the main studies on bone metabolism in the post Highly Active Antiretroviral Therapy (HAART) era, i.e. since 2003. We can conclude that the prevalence of osteopenia is increased in the HIV positive population (32%-54%); BMD changes are more pronounced in HIV-infected men than in the HIV-negative population.Osteoporosis in men preferentially affects cortical bone. Osteopenia in HIV-infected people is probably multifactorial resulting from diffferent aetiopathogenetic events.In the future we shall need many longitudinal and prospective studies to establish the correlation between BMD, HIV and HAART.

The Consensus Development Conference[1] defines osteoporosis as a "systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and fracture". Bone mineral density can be measured by dual X-ray absorptiometry (DXA) and the WHO defines osteoporosis as a BMD less than 2.5 standard deviations of the mean BMD of a sex-matched young healthy population; osteopenia is an intermediate category of bone loss defined as a T-score between -1 and -2.5.

Since the 1990s many papers have reported on bone metabolism changes even in the pre-HAART era and there has always been a suspicion that the virus was the underlying problem. After the advent of HAART the issue became more complicated because on the one hand HIV-infected patients can live longer but on the other they present the side-effects of treatment and older age. In addition, the changes in bone metabolism in this context appear to be a side effect of drugs.

In order to estimate the possible extent of bone changes in patients with HIV infection, five factors need to be considered: a) the phases of bone remodelling (activation>reabsorption>formation) take at least 100 days; b) 10% of the skeleton is continuously being renewed; c) it takes a year for bones to be completely mineralised; d) the skeleton needs a total of eight to ten years for complete renewal; e) from the age of 40 years osteoblast activity is no longer sufficient to replace the bone consumed by osteoclasts, so there is a deficit in the skeletal budget with a loss of bone mass. So now we can see the effect of eight to ten years of the action of a pathogen like virus or antiretroviral therapy, or both. In addition, we have to consider that our patients have been treated with antiretroviral therapy for an average of ten to 12 years, but in this time they have received different drugs at different dosages. This makes it really difficult to understand the true responsibility of a single drug or class of drugs in a retrospective study.

To disclose the true mechanisms underlying the bone metabolism changes in HIV means analysing all the metabolic problems present in HIV positive patients and understanding the different action and interaction between each drug, and between the drugs and the virus. In addition, we have to consider the cumulative effect of the drugs, the infection and all the additional treatments patients have received during recent years for opportunistic infections or other diseases and coinfections, without disregarding the well known risk factors for osteoporosis in the general population.

To start to understand the changes in bone metabolism in HIV-infected patients, we will review the main studies on bone metabolism in the post Highly Active Antiretroviral Therapy (HAART) era, i.e. since 2003. We will concentrate first on the prevalence of osteopenia and osteoporosis found in the HIV positive population, second on the difference between the patients treated with HAART or not, and lastly on the difference between the patients treated with PI or not.

In 2003 Bruera[2] addressed the changes in bone metabolism in HIV-seropositive patients by enrolling 142 subjects and determining bone mineral

density (BMD) by dual energy X-ray absorptiometry in total body, lumbar spine and proximal femur, measuring serum osteocalcin, d-pyridinoline, parathyroid hormone (THP), calcium and phosphate, and urine calcium. He demonstrated that BMD was significantly lower in HIV-seropositive patients than in controls in lumbar spine, proximal femur and total body, without significant differences among treatment-naive patients and either of the treatment groups (prevalence of reduced BMD%: HAART+: 69.2% vs HAART-: 54.5%). Only length of HIV infection and non specific therapy were associated with BMD decreases. In 2004 Amiel[3] published a valid study which had enrolled 148 HIV-infected men stratified according to treatment. This cross-sectional study did not show any deleterious effect of the treatment but did indicate a decrease in bone density in HIV+ patients irrespective of treatment (prevalence of reduced BMD%: HAART+: 77% vs HAART- 50%). This low bone density was in part related to the low body weight and was associated with increased bone resorption. In 2004 an Italian study[4] showed that HAART could be associated with osteopenia, even osteoporosis, and could exacerbate the loss in bone mass due to HIV infection itself. It was hypothesized that HAART may directly affect bone remodelling and/or indirectly affect vitamin D metabolism (prevalence of reduced BMD%: HAART+: 62.5% vs HAART-: 35%). In 2005 Garcia Aparicio[5] observed a greater prevalence of BMD in naïve patients with respect to treated patients (prevalence of reduced BMD%: HAART+: 53% vs HAART-: 61.5%). Lastly, in a meta-analytical review Brown[6] showed that HAART-treated subjects had a higher prevalence of reduced BMD than naïve subjects and the odds of osteoporosis was increased 2.4 times in HAART-treated patient compared with naïve patients.
Not all studies agreed on a negative effect of HAART on bone metabolism. In fact, Moyle et al. [7] observed that patients treated with NNRTI showed higher BMD than those treated with NRTI or PIs. Other authors described PIs as the "guilty" drug [7], whereas others could not find any difference among the various drugs used in HAART [8].

In 2003 Vescini[9] described a higher prevalence of osteopenia and osteoporosis than was to be expected in age-matched and sex-matched subjects, but he did not find any significance differences among different drug regimens (prevalence of reduced BMD%: PI+: 74.3% vs PI-: 88.6%). In 2003 Fernandez–Rivera[10] observed that loss of BMD is associated with PI therapy, low plasma albumin level, and male sex (prevalence of reduced BMD%: PI+: 49.2% vs PI-: 20%). In 2004 Dolan[11], investigating bone density in HIV-infected women, demonstrated that reduced BMD was 2.5 times more likely in HIV-infected women compared to healthy control subjects, but no differences were observed in the HIV-infected group by current and/or prior exposure to PI (prevalence of reduced BMD%: PI+:30.3 % vs PI-: 82.8%). On the contrary, in 2005 Yin[12] undertook a cross-sectional study enrolling 31 women, demonstrating that women treated with a PI-sparing regimen showed a higher prevalence of reduced BMD (prevalence of reduced BMD%: PI+:69.6 % vs PI-: 100%). Lastly, in a meta-analytical review Brown[13] showed that PI treated patients had a higher prevalence of reduced BMD compared with PI-untreated patients.

In 2006 Dolan et al. published a longitudinal analysis[14] in HIV infected women showing an HIV-related increase in bone mineral loss, but not a correlation between low BMD and PI treatment. In this population 41% of HIV-infected patients had osteopenia and 7% had osteoporosis. This study also showed a multifactorial pathogenesis of osteopenia in HIV patients that seemed to be related to smoking, low weight, duration of HIV infection and FSH alteration. In addition this group had an increased prevalence of oligomenorrhea and level of FSH as in the premenopausal period in spite of a median age similar to the uninfected group. The same group published another study[15] one year later to better explain the pathogenesis of mineral density loss in HIV-infected women. They emphasized the relation between loss of body weight and low BMD (more pronounced in white women), and also found a correlation between body composition and androgenic deficiency and a significant prevalence of oligomenorrhea in HIV patients, with androgenic deficiency being present in 20% of HIV-infected women. Again in 2007 Arnsten[16] found a prevalence of 54% of osteopenia or osteoporosis: 40% of osteopenia and 14% of osteoporosis in a population of aging men at risk for HIV. Among HIV-infected individuals the prevalence of BMD changes was greater (55%) but not statistically significant. After adjustment for other risk factors, the prevalence of osteopenia and osteoporosis remained slightly higher and statistically significant in the HIV group, whereas the proportion of men with osteoporosis was substantially higher than in general population (14%). This study also disclosed an increase in fractures in HIV patients but this was not statistically significant. There was an independent correlation between the known risk factors for osteoporosis like older age, non black race, lower body weight and low testosterone and BMD; neither HAART nor PI use were associated with BMD.
In the 14th CROI Overton et al.[17] presented the SUN study, a cohort of 562 HIV patients with 47% osteopenia and 11% osteoporosis. In multivariate analysis they found that "low BMD was associated with older age, male gender, lower body mass index, unemployment, and stavudine use; osteoporosis was associated with older age, non-white race, lower body mass index, longer duration since HIV diagnosis, and unemployment".
Similar findings were presented at the 15th CROI in a report by Yin's [18]: in a multicenter prospective study (WIHS) they performed a sub-study on 426 predominantly African American women (247 HIV+). They found a significantly lower baseline BMD in HIV+ subjects while bone loss over two years and bone turnover markers were similar between HIV+ and HIV-. They also found an elevated bone resorption but not an increase of bone loss in PI treated patients.
On the other hand, at the last CROI Guillemi et al.[19] found 54% of osteopenia and 13% of osteoporosis

in a study on 285 patients (89% male), with a correlation between abnormal BMD and low physical activity, alcohol consumption and current high pVL. They showed a correlation between abnormal BMD and the use of TDF but not PI. At the last IAS conference in Mexico City two studies reported similar findings. In one Calmy et al.[20] found 32% osteopenia and 44% elevated osteocalcin and 12% deficiency of Vitamin D in a cross-sectional study (153 patients, 150 men). Osteopenia was associated with current use of TDF but not with non-HIV factors. They found no evidence that proximal tubule renal disease is causally related to osteopenia. The second report was a retrospective case study by Horizon[21] that analysed 30 cases of fracture and disclosed a slightly higher incidence of foot fractures in HIV-infected patients on TDF- than non-TDF-containing HAART.
In recent years all published studies revealed the need to investigate the problem further. The latest prevalence study by the Aquitane Group[22] reported on a group of 492 patients (359 men) finding 53.7% osteopenia: 54.6% in men and 51.1% in women (50% premenopausal women and 54.8% menopausal); osteoporosis in 33.7% of men and 8.3% of women. They also found 10.2% pathological fractures, a relatively large number but difficult to compare with other data because no publication provides an estimate. In univariate analysis the cumulated exposure to PI drugs was significantly associated with bone abnormalities but this factor was not significant in the multivariate model. At the 15th CROI the same group[23] presented a study on HCV or HBV co-infected patients that confirmed an increased prevalence of low BMD in HIV patients (osteopenia 52.2% in men and 58.4% in women), but failed to observe any association with viral hepatitis.

The conclusions reached by the cited studies may appear discordant at a first sight, but some fundamental parameters should be addressed carefully. Some studies were confined to young homosexual men, whereas others involved only women or mixed patients. Results in yet other studies are related to BMI, smoking, calcium intake and other risk factors for osteopenia, but this is not always the case, preventing a comparison among studies. In addition not all studied investigated bone turnover. We can therefore conclude as follows:

- The prevalence of osteopenia is increased in the HIV positive population (32%-54%).
- BMD changes are more pronounced in HIV-infected men than in the HIV-negative population (Fernandez-Rivera, Overton, Cazanave).
- Osteoporosis in men preferentially affects cortical bone.
- Osteopenia in HIV-infected people is probably multifactorial resulting from diffferent aetiopathogenetic events.

Some open questions remain:

- Multifactorial pathogenesis: not only HIV or HAART are implicated in the increased bone mineral loss, but also many non HIV-related factors like: BMI, race, smoking, alcoholism, hypogonadism. Many studies have looked for a relation between these factors and the prevalence of BMD changes, but with different outcomes: Dolan, Arnsten and Overton found that they are related to low BMD, but a recent study by Calmy et al. failed to find this relation. A multifactorial origin is certain but it is difficult to establish the role of each factor.
- Many studies have shown a link between the HIV virus and BMD but it is hard to explain the role played by HIV in the pathogenesis and whether the action of antiretroviral drugs can in some way help to prevent osteporosis by combating the virus.
- Many studies show an effect of the drugs on bone metabolism (Vescini, Yin) but the role of PIs and whether TDF can also have a secondary effect on bone metabolism through kidney impairment (Calmy) remain unsettled issues.

When we study a patient now we must think first of his history, what kind of drugs he received during his life and in what dosages: experienced patients were initially treated with higher dosages than now. In addition, we must think of what additional treatments they received (steroids) and how long they have been HIV-infected (Overton). All these differences in treatment make the relevance of each drug very hard to establish.
Probably all these factors, HIV-related or not, play a role in the pathogenesis of BMD loss, but we do not know which is more important. In the future we shall need many longitudinal and prospective studies to establish the correlation between BMD, HIV and HAART. We must bear in mind that bone metabolism is pivotal in the daily management of our patients and may require an adjustment to the treatment.
One further issue remains: the bone effects of the new class of antiretroviral drugs such as integrase inhibitors and entry inhibitors: no study has yet analyzed the effects of these new drugs on bone metabolism, so ongoing attention is required to project the management of our patients in the right direction.

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