Biases in bone metabolism studies

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Abstract. An increase in life expectancy, contracted HIV infections in the elderly, comorbidity, and a discrepancy between real and biological age make BMD loss an unavoidable phenomenon in each patient. Both HIV and antiretrovirals amplify the age effect on BMD. Among N(n)RTIs, the effect of tenofovir on BMD seems to exceed the effect of other antiretrovirals, but we can find studies which confirm this observation, and other studies which doubt the conclusions and/or minimize the implications. This disagreement exists because there are a number of biases in all these studies that, unfortunately, compromise the conclusions. In the same analyses are men and women, different BMIs, different ages, different times of HIV infection before entering the trial, resulting in different biological ages, and especially different baseline BMD. All these biases together create a pool that is not homogeneous, having many variables, which complicates the correct interpretation of the results, especially in comparative studies between two pools. BMD in the studies is expressed as percentage loss during the follow-up, and not as the variation of absolute values of BMD: this feature may be deceptive regarding the real loss of BMD. Another bias is the approximate use, when defining BMD loss, of T-score even in non-menopausal women and in men younger than 50. Finally, another bias is the use of a different DXA machine to determine BMD. Prospective studies with a longer follow-up and without all these biases are urgently needed. (www.actabiomedica.it)

Key words: HIV, HAART, bone metabolism, osteoporosis, BMD, T-score, DXA

The skeleton, after a peak of bone mass in early youth, shows an unavoidable and unrelenting decrease in bone mineral density (BMD), which progressively contributes to the "frailty" concept so frequent in the elderly. In particular, after the peak of bone mass in our 20s, we physiologically lose 0.5% to 1% of BMD for each year of age (1).

The amount of peak of bone mass is, of course, the principal factor that determines whether a patient will develop osteopenia and/or osteoporosis and when.

The peak of bone mass is mainly defined by genetic factors, while external factors (e.g., viruses or drugs) contribute only 20% to 25%.

Therefore, an increase in life expectancy, contracted HIV infections in the elderly, comorbidity, and a discrepancy between real and biological age make BMD loss an unavoidable phenomenon in each patient, regardless of the regimen we use (2).

Consequently, many authors have performed studies to investigate BMD loss in HIV-infected patients, trying to distinguish and balance the different roles of the virus and the therapy (3).

As of today, many published studies confirm how HIV by itself can cause loss of BMD; HIV is the principal problem for the bone structure and the bone metabolism. HIV patients have a loss of BMD caused in primis by the virus, which increases the activity of the osteoclast cell and decreases the function of the osteoblast line, therefore intervening in correct bone-remodeling unit work, promoting a loss of BMD, which is amplified by age (4).

In fact, compared with HIV-uninfected controls, HIV-infected patients have 6.4-fold increased odds of reduced BMD and 3.7-fold increased odds of osteoporosis (3).

The answer, however, seems to be simple: if the virus is the problem for the bone, simply treat the virus.

Unfortunately, SMART trials have demonstrated that patients in the arm who discontinued HAART showed a better performance in terms of BMD compared with the group of patients in the arm who continued antiretrovirals (5). Other studies have further confirmed the SMART data: patients who discontinued therapy showed an unexpected restoring of BMD.

We can now accept that, unfortunately, HAART effects are more harmful to the bone than the virus damage is. Like the virus, antiretrovirals cause a loss of BMD by increasing the activity of the osteoclast cell and decreasing the function of the osteoblast line, therefore intervening in the correct bone-remodeling unit work. Patients who continue therapy show an increase in bone turnover markers, both neoformation and resorption (4).

Both HIV and antiretrovirals amplify the age effect on BMD; therefore, because HAART benefits, in general terms, clearly exceed HAART damage, the bone problem is unavoidable (6, 7).

In a patient with HIV infection, especially if the patient is on antiretroviral therapy, the skeleton biological age exceeds the patient's real age. Consequently, numerous published studies now intend to demonstrate which drug or regimen is the least dangerous for the bone to help design a friendly strategy. SMART data show a partial reversion in BMD loss, so there is great interest even in switch studies in patients with bone abnormalities.

Among N(n)RTIs, the effect of tenofovir (TDF) on BMD seems to exceed the effect of other antiretrovirals. Apparently, the skeleton of patients on TDF therapy is growing older faster than the skeleton of patients not on TDF. The skeleton of patients on TDF therapy shows an older biological age compared with patients not on TDF (8).

The scenario is more intricate and subtle if we analyze all the studies published on this interesting subject, because we can find studies like A5224s (9) or Assert (10), which confirm this observation, and other studies, like GS903E (11,12), which doubt the conclusions and/or minimize the implications (e.g., just a slight decrease in BMD that remains stable during follow-up).

This disagreement exists because there are a number of biases in all these studies that, unfortunately, compromise the conclusions.

All the studies on BMD are based on a DXA scan, and BMD is expressed as percentage loss, but in the same analyses are men and women, different BMIs, different ages, different times of HIV infection before entering the trial, resulting in different biological ages, and especially different baseline BMD. The mixture of all these parameters affects the final data: a 38-year-old man shows a different decrease in BMD compared with a postmenopausal woman, as does a man weighing 85 kg compared with a woman weighing 45 kg, or a patient with a longtime vs. a new HIV infection.

All these biases together create a pool that is not homogeneous, having many variables, which complicates the correct interpretation of the results, especially in comparative studies between two pools. Baseline BMD is, absolutely, more important than viral or HAART damage. A patient with a high BMD rarely will suffer an osteoporotic fracture even if the patient is in therapy with an osteotoxic regimen, but a patient with a low BMD risks an osteoporotic fracture even if in therapy with a friendly regimen.

BMD in the studies is expressed as percentage loss during the follow-up, and not as the variation of absolute values of BMD: this feature may be deceptive regarding the real loss of BMD. A patient with a high baseline BMD may have a higher absolute loss but a lower percentage loss compared with a patient with a low baseline BMD, who will have a lower absolute loss but a higher percentage loss. A discussion based only on percentage data, and not on absolute data, may generate incomplete conclusions.

The variations in BMD are generally expressed as percentage loss because a single patient must be his or her own control to monitor the course of his or her own BMD in follow-up, without being compared with different heterogeneous groups. Such a concept of "population BMD" does not exist.

Another bias is the approximate use, when defining BMD loss, of T-score (standard deviations compared with the peak of bone mass), which is valid only for menopausal women and for men over 50 years old. In all other circumstances, we have to use a Z-score (a T-score corrected for sex and age). Unfortunately, many studies continue to use a T-score even in non-menopausal women and in men younger than 50. This is a methodological mistake and does not promote understanding on whether or not the conclusions are likely.

Finally, another bias is the use of a different DXA machine to determine BMD. There are essentially two kinds of DXA machines: Lunar and Hologic. The difference in terms of BMD expression between the two machines is very wide (lower for Lunar, higher for Hologic), similar to what the FRAX algorithm (which is free online), used to estimate the fracture risk, shows at 10 years. BMD may seem normal or decreased if we use the two options without specifying which machine, mixing together Lunar and Hologic, omitting a specific phantom to continually calibrate the machine in multicenter studies.

BMD, as mentioned, is useful when a single patient is his or her own control to monitor the course of the patient's own BMD, and we can respect the results by using only the same kind of machine in all that patient's determinations. Of course, a trial with a Hologic machine will have numerically better DXA results compared with a study performed using a Lunar machine; therefore, we cannot put together in the same analyses Hologic and Lunar DXA. All the centers participating in a multicenter study must use either a Hologic or a Lunar DXA machine, and/or a phantom is needed to continually calibrate all the machines during the entire study.

Almost none of the studies in the Materials and Methods chapter explain these issues.

Because of these biases, we can assert that patients in therapy with TDF present an increase in bone turnover that is higher than for other regimens, but we cannot define with precision the exact amount of this phenomenon. Prospective studies with a longer follow-up and without all these biases are urgently needed.

References

1. Orwoll Es, Klei RF. Osteoporosis in men. *Endocr Rev* 1995; 16: 87-116.
2. Önen NF, Overton ET. Aging and HIV Infection: A Comparison Between Older HIV-Infected Persons. HIV and the General Population. *Clin Trials* 2010; 11 (2): 100-9.
3. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS* 2006; 20 (17): 2165-74.
4. Borderi M, Gibellini D. Metabolic bone disease in HIV infection. *AIDS* 2009; 23 (11): 1297-310.
5. Grund B, Peng G. Continuous antiretroviral therapy decreases bone mineral density. *AIDS* 2009; 23 (12): 1519-29.
6. Arora S, Agrawal M. HIV and bone loss. *Curr Osteoporos Rep* 2010; 8: 219-26.
7. Stone B, Dockrell D. HIV and bone disease. *Archives of Biochemistry and Biophysics* 2010; 503: 66-77.
8. Cotter AG, Powderly WG. Endocrine complications of human immunodeficiency virus infection: Hypogonadism, bone disease and tenofovir-related toxicity. *Best Practice & Research Clinical Endocrinology & Metabolism* 2011; 2: 501-15.
9. McComsey GA, Kitch D. Bone Mineral Density and Fractures in Antiretroviral-Naive Persons Randomized to Receive Abacavir-Lamivudine or Tenofovir Disoproxil Fumarate-Emtricitabine Along With Efavirenz or Atazanavir-Ritonavir: AIDS Clinical Trials Group A5224s, a Substudy of ACTG A5202. *The Journal of Infectious Diseases* 2011; 203: 1791-801.
10. Stellbrink HJ, Orkin C. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis* 2010; 51 (8): 963-72.
11. Gallant JE, Staszewski S. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA* 2004; 292 (2): 191-201.
12. Cassetti I, Madruga JV. The safety and efficacy of tenofovir DF in combination with lamivudine and efavirenz through 6 years in antiretroviral-naïve HIV-1-infected patients. *HIV Clin Trials* 2007; 8 (3): 164-72.

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