Diagnostic assessment of primary and HIV-induced osteoporosis

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ABSTRACT

Osteoporosis is a common, often disregarded, disease entailing an increased risk of bone fractures. Bone turnover is the main bone quality parameter, currently measured by biochemical markers, possibly flanked by traditional x-ray investigation. A series of observations on increasingly large cohorts of HIV patients have placed HIV infection among the causes of secondary osteoporosis. It is evident that high bone turnover, as in HIV-induced osteoporosis, involves cancellous bone earlier and to a greater extent, only compromising cortical bone much later. For this reason, BMD measurement in the spine is more likely to disclose osteoporotic disease than tests undertaken in femur. Much progress has been made since the first reports of HIV and HAART-induced bone damage, but we have yet to reach an adequate diagnostic definition.

Primary osteoporosis (post-menopausal and senile)

Osteoporosis is a common, often disregarded, disease entailing an increased risk of bone fractures. The lifetime risk of fractures involving the wrist, spine or femur for a 50-year-old woman is estimated to be around 40%, whereas the risk for a man of the same age is around 13%. When other bones are considered (e.g. humerus, tarsal phalanges, ribs, etc.) the lifetime risk for a 50-year-old woman reaches 70% (1).

Osteoporosis is a systemic condition characterized by both quantitative and qualitative alterations that reduce bone strength (2) (Table 1). The quantitative component of bone strength can easily be evaluated by dual X-ray absorptiometry (DXA) that can measure bone mineral density (BMD), a parameter widely demonstrated to predict fracture risk (3). BMD is commonly reported in terms of T-score that will establish the densitometric diagnosis of osteopenia and osteoporosis according to the WHO Classification (4). However DXA-based diagnosis cannot replace clinical evaluation which must ascertain the aetiology of osteoporosis in case of a pathological T-score. Thorough history-taking, clinical assessment and a few simple laboratory tests (haemochrome, liver and kidney function, serum protein electrophoresis, VES, blood and urine calcium, phosphoraemia and a urine test) osteoporosis secondary to other illnesses can be easily ruled out. At this point a diagnosis of primary osteoporosis can be established, most commonly post-menopausal and senile osteoporosis.

Table 1. Components of bone strength

Bone quantity	Bone quality
• Mass • Mineral density • Size	*Structural properties* • Macro-architecture – geometry • Micro-architecture – Connectivity – Thickness/Cortical porosity *Material properties* • Mineralization • Collagen • Micro-damnages *Bone Turnover* • Resorption • Formation

Bone turnover is the main bone quality parameter, currently measured by biochemical markers, possibly flanked by traditional x-ray investigation. Bone turnover markers include markers of both bone formation and resorption offering indirect measurements of osteoblastic and osteoclastic activity respectively. Some studies have demonstrated that bone turnover markers, namely those of bone resorption, serve as a useful tool for fracture risk assessment (5,6). The predictive value of these markers per-

sists even after adjustment for BMD values, making them a risk factor independent of bone mass (7-9).
Traditional x-ray examination, by means of lateral views, will disclose any spinal deformities that represent an important predictive factor for the risk of subsequent fractures. X-ray of the femur may also yield information on bone resistance. A study by Cheng et al. on femurs from 64 cadavers (10) demonstrated that both the length and width of the femur neck correlated significantly with bone resistance ($r^2 = 0.24, 0.22$, respectively).
In the light of these considerations, BMD measurement alone is not sufficient to establish a diagnosis of osteoporosis that requires an overall medical assessment and clinical classification of the patient before instituting medical management designed to reduce the fracture risk.

Osteoporosis secondary to HIV infection

In recent years, a series of observations on increasingly large cohorts of HIV patients have placed HIV infection among the causes of secondary osteoporosis (11). The osteotoxic effect is exerted not only by the HIV virus, but also by highly active antiretroviral therapies (HAART). Among the drugs used for HAART, evidence is accumulating on the osteotoxic effect of N(n)RTI by means of mitochondrial DNA polymerase γ inhibition, and PIs by renal α-1 hydroxylase inhibition and possibly aromatasis.
Whatever the aetiopathogenesis of HIV-induced osteoporosis, literature reports contain a remarkably varied prevalence of osteopenia and osteoporosis (Table 2). Some papers report osteopenia in around 3% of patients studied, whereas others found osteopenia and osteoporosis in more than 80%. This vast range of prevalence is probably related to the different bone sites investigated, in some cases only the spine (mainly confined to cancellous bone), in others only the femur (mostly cortical bone), in yet others both bone sites. The human skeleton is composed of two different types of bone tissues: cancellous bone comprising around 20% of the total, and cortical bone making up the remainder. Cortical bone is responsible for most support functions, whereas cancellous bone is mainly involved in the maintenance of mineral homeostasis. It is evident that high bone turnover, as in HIV-induced osteoporosis, involves cancellous bone earlier and to a greater extent, only compromising cortical bone much later. For this reason, BMD measurement in the spine is more likely to disclose osteoporotic disease than tests undertaken in femur.
Another reason for the wide range of BMD reported in the literature depends on the different machines used for densitometric measurement. All apparatuses measure BMD, but the T-score is calculated on the basis of databases inserted in the densitometer's memory. In other words, each machine contains reference curves devised from different populations, so that the calculated T-score will vary in different tests conducted on different densitometers (12).
Lastly, it should be recalled that HIV-positive patients are younger than those who usually present with osteoporosis and also include a high percentage of men (as opposed to the normal cohorts of women in menopause). The recent guidelines devised by the "International Society for Clinical Densitometry" (ISCD) recommend using the T-score with the diagnostic cut-off value specified by the WHO only for women in menopause. Although definitive data are lacking, it is generally accepted that the same method be applied to men over the age of fifty. The problem arises with fertile women and young men, i.e. the vast majority of HIV-positive patients. For these subjects aged under fifty years, diagnosis is recommended using the Z-score that compares the patient's BMD to that of a healthy age- and sex-matched population. However, the Z-score has no clear cut-off value for osteopenia and osteoporosis and the following scores are recommended: patients with values lower than – 1 are classified as having low bone mass, while a severe bone mass reduction is identified by Z-score values lower than – 2.
Although HIV-induced osteoporosis has already been identified as a secondary bone disease, laboratory tests may yield further useful information. As stated above, bone turnover markers increase the positive predictive power of BMD on fracture risk. In addition, we demonstrated that the response of bone resorption markers to anti-resorptive treatment occurs earlier than the response disclosed by BMD measurement (14). Plainly this reflects

Table 2. Prevalence of bone loss and osteoporosis in HIV-positive patients

Authors	Year	No. patients	Osteopenia	Osteoporosis
Paton et al.	1997	45	3%	---
Tebas et al.	2000	124	39%	11%
Hoy J.	2000		28.4%	9.5%
Carr et al.	2001	221	50%	
Knobel et al.	2001	70	66.5%	22.2%
Moorea et al.	2001	105	58%	13%
Nolan et al.	2001	183	38.2% (PIs) 40% (no PIs)	18.3% (PIs) 7.7% (no PIs)
Mondy et al.	2003	135	46% osteopenia or osteoporosis	
Vescini et al.	2003	70	40% (lumbar) 45.7% (femur)	8.6% (lumbar) 10% (femur)
Dolan et al.	2004	84	54%	10%
Ozcakar et al.	2005	27	51.8%	33.3%

the important role of bone turnover markers in predicting skeletal events at least in candidates for bisphosphonates therapy.

Conclusions

Much progress has been made since the first reports of HIV and HAART-induced bone damage, but we have yet to reach an adequate diagnostic definition. First and foremost, the true prevalence of osteopenia and osteoporosis in HIV-positive patients could be underestimated due to the improper use of the T-score for diagnosis, as already emerged in our 2003 paper (15). In addition, the true incidence of osteoporotic fractures in this particular population remains unsettled. Lastly, laboratory tests are not routinely used in the diagnostic work-up for osteoporosis.
In conclusion, all these considerations demonstrate how HIV-induced osteopenia remains a poorly defined clinical entity requiring further investigation to shed light on its true impact.

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