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Bone Metabolism and HIV Infection

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1. Introduction

Osteoporosis (OP) is the most widely spread metabolic osteopathy in the Western world, and is defined as a generalised state of the skeletal structure, characterised by a low bone mass and microarchitectural alterations, with an increase in bone fragility and risk of fracture (1). OP is now considered as an evolutive disorder affecting both the mineral and organic components leading to a progressive reduction in bone density, due to an imbalance in the regulation of hormones, which normally regulates the skeletal tissues (2). There are numerous classifications of OP in existence based on its pathogenesis , age of onset, association with other pathologies and pharmacological treatment or skeletal districts involved. Alongside primary OP is the heterogeneous group of secondary OP, which is either the consequence of the core disease or of the use of drugs. HIV infection has been shown to play an important role in the development of OP (3) and high prevalence of both osteopenia (OPe) and OP have been reported in subjects with chronic HIV infection (4). Loss of body weight, low body mass index (BMI) and diminished functional capacity are among some of the risk factors which, to a large extent, contribute to the loss of bone tissues in subjects suffering from chronic HIV infection (2-8).Furthermore, the drugs used to treat HIV+ patients can also interfere with bone metabolism and contribute to loss of bone mass (16). A reduction in bone mineral density (BMD) was observed in both HIV+ patients with hypogonadism and in those without (9-11). OP seems to be most frequently observed in subjects undergoing intense antiretroviral therapy, however, the mechanism by which antiretroviral treatments interfere with bone metabolism has not yet been clearly demonstrated.

The success of highly active antiretroviral therapy (HAART) has dramatically increased the life expectancy of HIV+ patients in the developed world, however, their use has been associated with a range of side effects and complications. As people with HIV now live longer, bone disease is among the metabolic complications presenting physicians with new challenges in the management of the HIV+ patients (12). Although, OP is the most common bone disease described in HIV, but osteomalacia, usually in association with Fanconi's syndrome or in patients treated with tenofovir, is also reported (15).

The reduction in bone mass and the disruption of bone architecture increases the risk of bone fracture leading to disability, morbidity and mortality especially in the older population. One in two women and one in five men over the age of 50 years will suffer a fracture due to OP during their lifetime (13). There are concerns that as the HIV+ population ages, increased rates of bone loss may give rise to an 'epidemic' of fragility fractures (17).

Evidence is needed to inform judicious use of bone protective agents so that this situation can be avoided.

2. Does HIV cause low bone mineral density?

Validated risk factors for reduced BMD and fragility fracture are well established for the general population (19). They include,old age, low BMI, previous fragility fracture, low BMD at the femoral neck, parental history of hip fracture; glucocorticoid exposure; rheumatoid arthritis; current smoking; alcohol consumption of more than 3 units per day; hypogonadism, including post-menopausal status in women; prolonged immobility; malabsorption and liver cirrhosis (20). In addition, other well reported associations exist, including vitamin D deficiency, opiate (21) and other substance dependence (22) and the use of selective serotonin uptake inhibitor (SSRI) antidepressants (23). Some of the risk factors for OP described in the general population are also prevalent in people with HIV infection. The HIV+ population also has high rates of vitamin D insufficiency, high prevalence of smoking, alcohol abuse and injection drug use, opiate use and depression requiring SSRI treatment that are also risk factors for OP (25). Patients presenting late in their illness with AIDS usually have a low BMI. Immune reconstitution inflammatory syndrome (IRIS), which arises when HAART-associated immune reconstitution leads to an unmasking or worsening of features of infections such as tuberculosis, may require prolonged courses of glucocorticoid therapy (26), as may treatment of malignancies. Chronic diarrhoea resulting in malabsorption and nutritional deficiency can occur secondary to opportunistic infections or HIV directly. Androgen deficiency was common in the pre-HAART era in men presenting with AIDS-associated wasting (27) and is still seen in HIV-infected men on HAART presenting with weight loss (28). Low testosterone levels have also been reported in association with intravenous drug use (29). Of note, menstrual abnormalities are not more prevalent in HIV-infected women compared with non-infected women (30). There are growing numbers of studies reporting an increased prevalence of vitamin D deficiency in HIV-positive individuals compared to HIV-negative controls. Other studies have also demonstrated reduced 25-hydroxyvitamin D serum levels in HIV+ individuals taking HAART compared to age- and sex-matched HAART-naïve HIV+ individuals, with non-nucleoside reverse transcriptase inhibitor (NNRTI) use and, moreover, cumulative exposure to efavirenz (but not nevirapine) being specifically implicated. Considering the high prevalence of the above risk factors in the HIV-infected population, it could be argued that the increased prevalence of decreased BMD in HIV-positive individuals is not surprising. It is very challenging, however, to separate HIV-specific factors from the confounding effect of traditional risk factors which are over-represented in the HIV-positive population.

HIV-specific risk factors. As well as establishing the contribution of known OP risk factors within the HIV-positive population, cross-sectional and longitudinal studies have also related changes in BMD to HIV-specific factors, for example duration of HIV infection, HIV viral load and CD4 cell count, to determine whether these represent independent risk factors for reduced BMD in the HIV-positive population and consequently whether HIV infection is a risk factor for reduced BMD in its own right. The extent of the rise in CD4 cell count was directly proportional to the BMD increase at the lumbar spine in one longitudinal study of patients on HAART (31). Similar findings were seen in another longitudinal study, although without adjustment for simultaneous rise in BMI (28). The BMD increase in these two studies was also independently associated with having an undetectable HIV viral load.

In support of these findings a high HIV viral load at the time of assessment by Dual Energy X-Ray Absorptiometry (DXA) correlated positively with reduced BMD in one cross-sectional study (32), although neither high HIV viral load nor low CD4 count were associated with reduced BMD in other studies (33). A low nadir CD4 cell count has been shown to be an independent risk factor for both reduced BMD and increased fracture incidence after adjustment for BMI (34). Time from date of diagnosis and prolonged exposure to unsuppressed HIV was also found to be an independent risk factor for loss of BMD in three studies (33).

3. HIV-1 infection has direct influence on bone turnover

The mechanical competence of bone is maintained by the process of bone remodelling, which consists of the removal of old bone by osteoclasts and its subsequent replacement with new bone by osteoblasts. In young adult skeleton, the amounts of bone resorbed and formed are similar, thus maintaining bone mass. Bone loss may occur in OP as a result of increased resorption, decreased formation or a combination of the two. In age-related bone loss in women, both mechanisms play a role, whereas in men, reduced bone formation is the predominant changes (49).The cellular mechanisms underlying bone loss in HIV+ individuals are not well defined, although in one study, reduced bone formation and turnover were reported in iliac crest biopsies (49,50). The association between chronic inflammatory conditions and OP is well documented and receptor activator of NFkB ligand (RANKL), the key mediator of osteoclast activity, is produced by activated T cells (46). Even in the asymptomatic phase of HIV infection, levels of inflammatory cytokines such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor alpha (TNFa) are increased, and these cytokines also stimulate bone resorption (51). TNFa has also been shown to mediate apoptosis of human osteoblasts in response to HIV gp120 (52). Studies recently reported that levels of RANKL were higher in HIV-infected men and correlated with reduced BMD. Osteoblast and osteoclast function is influenced by a number of factors during HIV-1 infection, including pro-inflammatory cytokines such as TNF-a, expression of receptor of activated NF-kB ligand (RANKL) and osteoprotegerin (OPG), vitamin D and calcium metabolism and hormone levels (36). Although there is not convincing evidence that osteoblasts or osteoclasts are directly infected, their function may be modulated by a variety of HIV proteins. The HIV envelope glycoprotein, gp 120, can induce TNF-a dependent apoptosis of osteoblast cell lines or primary cells (37); however many HIV-mediated effects occur without affecting cell viability. Inflammatory conditions modify bone metabolism, including a variety of factors released by T-cells and macrophages such as TNF-a, IFN-c, IL-4, macrophage inflammation protein-1 (MIP-1) and RANKL. Markers of bone resorption in advanced HIV infection correlate with TNF-a levels (38). During HIV infection the cytokine profile favors TNF-a expression and increased viral replication, whilst there is a shift towards a TH2 cytokine balance, with decreased production of IFN-c (34). In turn enhanced TNF-a levels increases expression of RANKL with resulting stimulation of osteoclast activity (39). A number of studies suggest HIV proteins can shift the OPG/RANKL ratio in favour of RANKL-mediated osteoclastic activation (40). HIV Vpr (viral protein R), a factor needed for viral replication being required for the nuclear import of the HIV-1 pre-integration complex, up-regulates RANKL, potentiating glucocorticoid-induced stimulation of RANKL (41). gp120 also stimulates RANKL (42). ARV naïve HIV-positive individuals have increased serum RANKL levels and reduced OPG/RANKL ratios, which correlate negatively with the

HIV viral load and the Z-score obtained by densitometry (43). RANKL is not only produced by osteoblasts but also by activated T-cells, which represent a likely source of enhanced RANKL expression in light of their increased numbers during HIV infection. Although the natural inhibitor of RANKL, OPG, is also enhanced in the serum of ARV naïve individuals, increased binding of OPG to another factor up regulated by HIV, TNF-related apoptosis-inducing ligand (TRAIL), in preference to RANKL, limits its availability to inhibit osteoclast activation by RANKL (44). RANK (receptor of activated NF-kB) signalling via tumour necrosis factor receptor-associated factor 6 (TRAF-6) facilitates nuclear factor kappa B (NF-kB) activation and phosphorylates (activates) c-Jun NH2- terminal kinase (JNK) 1 and Akt facilitating osteoclastogenesis. gp120 may also stimulate RANKL via activation of extracellular signal-regulated kinase (ERK) signaling. Nevertheless the specific RANK signaling events activated by HIV-1 are still being delineated. RANKL appears to limit the susceptibility of mitochondria to oxidative stress induced dysfunction in response to nucleoside reverse transcriptase inhibitors (NRTIs) by mechanisms that do not involve alterations in levels of mitochondrial superoxide dismutase (SOD) (45). These observations, in macrophage cell lines, if replicated in osteoclasts, may suggest a potential mechanism for enhanced osteoclastogenesis in response to RANKL could therefore be maintenance of mitochondrial metabolism despite increasing cell stress and therefore maintenance of osteoclast viability and prevention of apoptotic death (46). HIV proteins gp120 and the gag structural protein p55 suppress osteoblast activity in cell lines with up-regulation of the transcription factor RUNX-2 and decreased release of RANKL. p55 also suppresses osteoblast differentiation from mesenchymal stem cells (47).

4. Does HAART increase the risk of osteoporosis?

Protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) have been the agents most widely investigated as causes for reduced BMD in HIV+ populations. However, consistent evidence for their effects is lacking and it is increasingly recognized that these may be drug rather than class-specific (48). Potential mechanisms by which antiretroviral might negatively affect BMD have been identified in vitro. Some PIs have been shown to inhibit osteogenesis and increase osteoclastogenesis, whereas others may decrease bone loss (53). Metabolic and morphologic changes have been described in patients with HIV infection receiving antiretroviral therapy (ART), including alterations in body fat distribution, dyslipidemia, lactic acidosis, glucose metabolism abnormalities, and bone metabolism abnormalities. The etiologies of these disorders are being investigated and are likely to be multifactorial. It is clear, however, that ART plays a significant role in these alterations.

5. Pathophysiology of osteoporosis in HIV patients

In the light of these facts, we set out to determine the incidence of OPe and OP, within a population of subjects suffering from chronic HIV infection, by calculating the biochemical parameters using the ultrasonic densitometer. The Quantitative Ultrasound Densitometry (QUS) was chosen for the fact that this exam enabled us to predict the risk of fractures, also for the vertebrae, comparable to the DEXA method (56-58), in addition to its low cost and feasibility. This study consisted of 26 HIV+ patients (mean age 47.9 ± 12.8), with a average duration of infection equal to 6.7 ± 4.8 years and seropositive duration ranging from 6

months to 16 years. This group of patients did not exhibit any associated diseases, while the BMI was equal to 24.82±1.45. No other type of pharmacological treatment was introduced other than the one for HIV infection. In this group of patients, 6 exhibited illnesses associated with HIV, such as: *pneumocystis carinii* infection, hepatocellular carcinoma, tuberculosis, cerebral neoplasia and HIV-related encephalitis. From our samples, 4 belonged to class C under the CDC classification (Centers for Disease Control – USA; 23) (59).

The aim of our study was to determine has been to observe whether the presence of seropositivity for HIV could constitute to the development of OPe and/or overt OP. Meanwhile, our group of patients fell within the age bracket well below the limit for both post-menopausal and senile OP, with a superimposable average age for either sex. The different aspects evident at the bone level during the course of HIV infection stress that , in the various forms of genesis the IPs (Protease inhibitors (PIs) seem to play a causal predominant role. Other attributable factors are in play, like the possible interference of hormonal factors (behavioural and/or nutritional) directly correlated with the state of infection, but also the dysmetabolic effects of the antiretroviral drugs depending on the mechanism and the time involved. The protocols of the HAART therapy on the hand lead with a decisive improvement in the life expectancy and quality of life of HIV+ patients, but expose to toxic effects, which generally become more frequent and severe as the treatment is prolonged, and may take effect within diverse metabolic areas. As far as the skeletal structure is concerned, such effects can seriously impair the status of bone metabolism with pathological pictures of variable graveness, ranging from OPe to osteonecrosis (with a higher risk of developing pathological fractures). It is of extreme importance to have one or more of the instruments to safely and easily individualise the alterations of bone resistance readily available for diagnostic procedures aimed at various aspects of the disease and the adverse reactions of the antiretroviral therapy, before they advance into significant clinical events. In fact, a prompt diagnosis can allow for the implementation of more efficient therapeutic and prophylactic measures. Bone resistance must be considered, in a modern sense, as a fundamental characteristic of the bones themselves, which contribute to quantitative (bone density) and qualitative factors (structural properties, biomechanical properties, bone turnover). Our study also included an ultrasonometric bone assessment and biochemical assessment – in terms of neoformation marker and bone resorption markers. Motivations which have led us to use the ultrasonic densitometer to calculate the variations of bone resistance in the population in question were based on the grounds of employing a procedure which was safe and non invasive. This decision was also based on the possibility of obtaining accurate information on all the factors influencing bone resistance (biomechanical competence and elements associated to bone quality). In the course of our study, the ultrasonic densitometer also proved to be a highly sensitive diagnostic safeguard, allowing us to individualise an elevated incidence of cases of OPe/OP in HIV+ subjects. Analysis of the ultrasonometric parameters according to sex does not show significant variations, except for the broadband ultrasound attenuation (BUA), which seems to be significantly lower in females with respect to males. Significant variations can also be observed in relation to the duration of HIV infection, with ultrasonometric values highlighting its inclination towards OPe/OP with an increase in the number of years of infection-disease. Significant, indeed, is the reduction in the values of BMD relative to the duration of infection; proving the hypothesis that HIV inhibits osteoblastic activities and triggers osteoclastic activities, resulting in a negative skeletal balance, with an annual reduction in BMD values equal to approximately 1%. As for the dosage of sieric osteocalcin,

particularly the bone neoformation index, the data obtained does not allow for the complete explanation of the significance of the diagnosis, however, it does highlight the elevated sieric concentration in women after about 10-12 years of seropositivity, conferming the ultrasonometric results showing the presence of the aggressive processes of bone mineralisation. The assessment of other bone turnover markers does not reveal any significant variations – in terms of resorption marker – in subjects belonging to diverse classes under the CDC classification, with the exception of d-PYR in the group with the most serious conditions: this marker showed an unexpected lower mean level compared to the groups with patients in less aggressive situations. Although the results obtained from our study does not enable us to reach a definitive conclusion regarding the origin of the pictures of alterated bone mineralisation during the course of HIV infection, it does emphasise the considerable incidence, and destined to increase, thanks to the ever improving life expectancy as a result of more efficient antiretroviral therapies which are better tolerated by the patients. This problem presents a particularly serious connotation in younger subjects where the consequence of a chronic reduction in bone quality and quantity could result in irreversible disability. Bear in mind that it is, therefore, advisable to predispose accurate protocols when monitoring the skeletal development in these patients, based on the use of biochemical and instrumental research. Each patient should be followed with an individual programme, appropriately prepared based on age and personal characteristics, along with regular physical activities aimed at strengthening the skeletal muscles. It should also include a healthy diet, with particular reference to daily intakes of calcium and Vitamin D (60).

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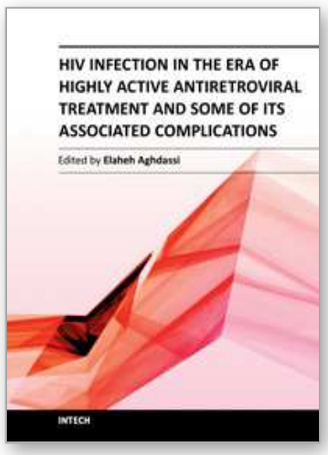

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Human immunodeficiency virus (HIV) infection is a complex illness affecting the immune system. Acquired immunodeficiency syndrome (AIDS) is an advanced form of HIV infection in which the patient has developed opportunistic infections or certain types of cancer and/or the CD4+ T cell count has dropped below 200/µL. More than 40 million persons around the world are infected with HIV, with approximately 14,000 new infections every day. The disease causes 3 million deaths worldwide each year, 95% of them in developing countries. Optimal management of human immunodeficiency virus requires strict adherence to highly active antiretroviral treatment (HAART) regimens, but the complexity of these regimens (e.g., pill burden, food requirements, drug interactions, and severe adverse effects) limits effective treatment. However, more patients with HIV are surviving longer today because of these drugs. This allows further study of commonly associated adverse effects. These may affect all body systems and range from serious toxicities to uncomfortable but manageable events. This book reviews some of HAART-related metabolic and neurological complications.

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