An Increased Risk of Osteoporosis during Acquired Immunodeficiency Syndrome

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Abstract

Osteoporosis is characterized by decreased bone mineral density and mechanistic imbalances of bone tissue that may result in reduced skeletal strength and an enhanced susceptibility to fractures. Osteoporosis in its most common form affects the elderly (both sexes) and all racial groups of human beings. Multiple environmental risk factors like acquired immune deficiency syndrome (AIDS) are believed to be one of the causes of osteoporosis. Recently a high incidence of osteoporosis has been observed in human immunodeficiency virus (HIV) infected individuals. The etiology of this occurrence in HIV infections is controversial. This problem seems to be more frequent in patients receiving potent antiretroviral therapy. In AIDS, the main suggested risk factors for the development of osteoporosis are use of protease inhibitors, longer duration of HIV infection, lower body weight before antiretroviral therapy, high viral load. Variations in serum parameters like osteocalcin, c-telopeptide, levels of elements like Calcium, Magnesium, Phosphorus, concentration of vitamin-D metabolites, lactate levels, bicarbonate concentrations, amount of alkaline phosphatase are demonstrated in the course of development of osteoporosis. OPG/RANKL/RANK system is final mediator of bone remodeling. Bone mineral density (BMD) test is of added value to assess the risk of osteoporosis in patients infected with AIDS. The biochemical markers also aid in this assessment. Clinical management mostly follows the lines of treatment of osteoporosis and osteopenia.

Key words

Osteoporosis, AIDS, HIV, Bone mineral density, HAART, Protease inhibitor, OPG/RANKL/RANK

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1. INTRODUCTION

Osteoporosis is a significant cause of morbidity and mortality worldwide with an estimated ten million people in the United States already living with this disease [1]. It is a disease characterized by abnormalities in the amount and architectural arrangement of bone tissue, which lead to impaired skeletal strength and an increased susceptibility to fractures [2]. Bone is composed of organic component consisting of collagen which gives bone its flexibility, and a mineral component that includes calcium and phosphate salts, which combine to form hydroxyapatite crystals and add hardness to the collagen matrix. Osteoporotic condition manifests reduced bone mass with a loss of both collagen and minerals. Inspite of this loss, the collagen - calcium ratio is maintained at normal levels. However the reduced levels of both collagen and calcium compromise the bone strength leading to risk of fracture. Osteoporosis is characterized as either primary or secondary. Primary osteoporosis occurs in both sexes at all ages but often follows menopause in women and occurs later in life in men. In contrast secondary osteoporosis is a result of medication, other conditions, or diseases [3]. Many of the commonly occurring diseases like endocrine disorders, malabsorption disorders, bone marrow disorders and inflammatory diseases were reported to be associated with osteoporosis. In addition AIDS or HIV infection is also reported to play an important role in osteoporosis. In the recent days, high incidence of osteoporosis has been observed in HIV infected individuals [4-8].

AIDS is one of the known multiple environmental risk factors of osteoporosis [9]. HIV infection is associated with numerous metabolic and endocrine complications, leading to loss of appetite and hypogonadism. Medication during therapy also affect bone metabolism and contribute to bone loss [4,5]. Bone remodeling process is altered in HIV-infections which contributes to bone loss [6]. Weight loss, reduced lean body mass, and impaired functional capacity are the factors which may further predispose HIV infected individuals with wasting to bone loss. Reduced bone mineral density (BMD) has been demonstrated in HIV-infected men with hypogonadism [7] as well as in non-wasted HIV infected men [8]. Anabolic effects of testosterone and progressive resistance training therapy on lean body mass and muscle function in men with AIDS wasting have recently been reported [10,11]. Osteoporosis problem seems to be more frequent in patients receiving potent antiretroviral therapy, although a specific contribution of the drugs used in different combination regimens is yet to be established [12-15].

The introduction of highly active antiretroviral therapy (HAART) with the use of protease inhibitors (PI) has resulted in significant reductions in morbidity and mortality from HIV infection in recent years [16,17]. 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 [18-24]. These toxicities include the development of diabetes mellitus, insulin resistance, hyperlipidemia, lipodystrophy and lactic acidosis [19-24]. The current review focuses on the possible factors that affect bone turnover and cause related bone disorders in AIDS.

2. EPIDEMIOLOGY OF OSTEOPOROSIS

A. MAGNITUDE OF THE PROBLEM

The number of people considered to have osteoporosis depends entirely on the way the condition is defined in practice. A committee of the World Health Organization (WHO) recommended the definitions shown in Table-1 [25]. It is possible to diagnose and treat osteoporosis (bone density levels more than 2.5 standard deviations (SD) below the young normal mean) prior to the occurrence of fractures (established osteoporosis). This avoids the need to restrict treatment to end-stage disease, where it may be of limited effectiveness. It also circumvents the conceptual confusion that previously existed when a fracture occurred, without any change in underlying bone density [26]. Women with bone density levels between 1.0 and 2.5 SD below young normal mean levels have low bone mass, or osteopenia. Thus perimenopasual women with bone density that is 1 SD below the young normal mean might not have pathologically low bone mass but still they are at sufficiently high risk of fracture over their remaining lifetime that preventive therapy is indicted [27]. This is particularly important since currently available treatments can conserve existing bone mass but cannot restore osteoporotic bone to biomechanical normality [28].

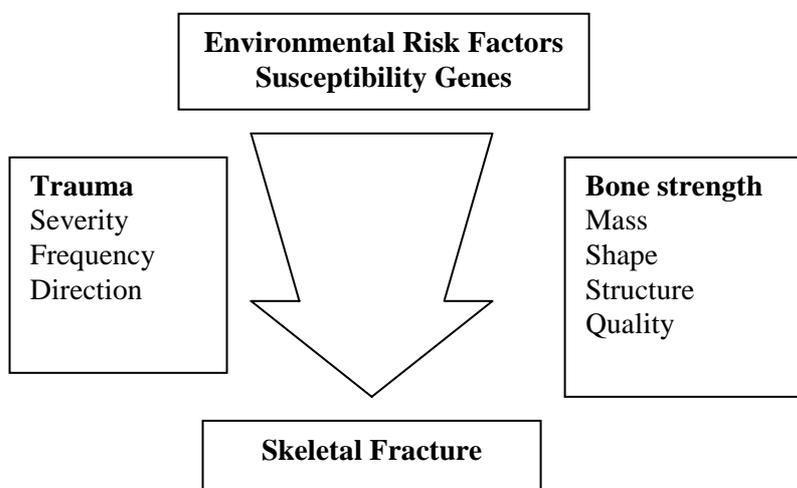**Table 1**: World Health Organization Definition of Osteoporosis

Bone Disorder	Bone Density in standard deviation (below the young adult mean)
Normal	>1
Osteopenia	1-2.5
Osteoporosis	>2.5
Severe Osteoporosis	>2.5 with fracture

Source of table – Reference [25]

B. RISK FACTORS FOR OSTEOPOROSIS IN AIDS

The risk factors for osteoporosis are fairly straight forward (fig 1).

Fig.1 Schema of the object of environmental and genetic risk factors on the interaction between bone strength and trauma that leads to osteoporotic fracture. Source of Fig. - Reference [29]
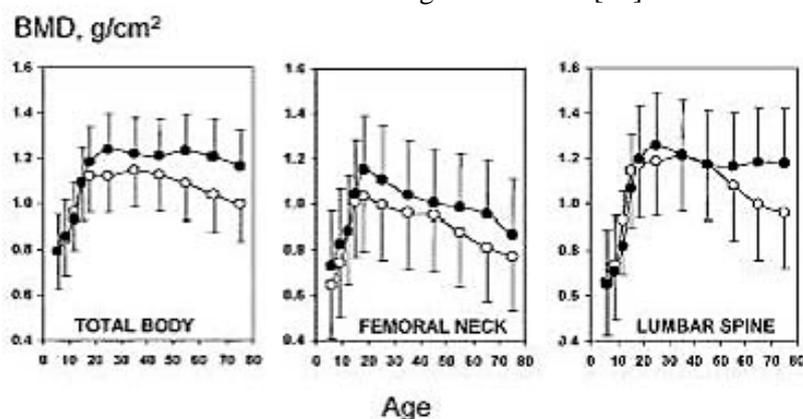

Osteoporosis in its most common form occurs in both the sexes of elderly and all racial groups affecting the BMD. The variations in bone mineral density in men and women are shown in fig. 2 [29]. A person's bone mass later in life is determined by the maximal bone mass achieved in young adulthood, as well as by the subsequent rate of bone loss. At the of age 70 years, these two determinants of bone mass are equally important [30]. The bone loss results from age-related factors that occur universally in the population and account for slow bone loss over life in both sexes. An accelerated phase of bone loss is associated with the menopause in women and hypogonadism in some men; and from medical and surgical conditions that produce secondary osteoporosis [28]. Thus race and sex differences in osteoporosis are explained in part by the heritability of skeletal size. Bone mass is greatest in those of African heritage, who have the lowest fracture rates, and is least in Caucasian women of Northern European origin, who have the highest fracture rates [32]. Similarly the accelerated phase of bone loss in perimenopasual women is superimposed upon the slower, age-related bone loss seen in both sexes and explains in part the two fold higher incidence of fractures among women than men later in life [28]. Other genetic risk factors play a major role in the heritability of many components of bone strength. There are a small number of cytogenetic [32,33] and monogenetic diseases causing osteoporosis [34-39]. Quantitative traits in bone strength in the normal population do not conform to a monogenetic mode of inheritance. The common form of osteoporosis is generally considered to be polygenic arising from the interactions of common polymorphic alleles at quantitative trait loci (QTL) with multiple environmental factors. Finding the genes underlying osteoporosis typically requires identification of its key heritable phenotypes and demonstrating in family and population studies that these phenotypes are coinherited with specific alleles. With progress in developing statistical methods to detect QTL and biochemical techniques to identify and map abundant

polymorphisms throughout the genome studies [40,41] for identifying the susceptibile genes for osteoporosis made easy for timely study.

Microbial genome sequencing is likely to play an increasingly important role in the analysis of newly discovered human genes and provide further clues to the molecular basis of the diseases [42]. Because of the close correspondence among mammalian genomes, it is a hope that identification of the genes underlying bone strength in mammals such as the mouse [43] will be of major assistance for human studies. The identification of susceptibile genes for osteoporosis is expected to be a major contributing factor toward the long-term goal of understanding the molecular biology of the normal variation in bone strength and how it may be modified to prevent osteoporotic fractures. As with all genetic studies in humans, these scientific advances are need to be made in an environment of legal and ethical safeguards that are acceptable to the general public [44].

Fig 2. Normal variation (mean and 2 8D) and change in BMD with age in healthy men (black circle) and women in (open circle) (Normal population Data base, DPX-IQ Reference Manual, Documentation Version 5/96, Lunar Corp., Maidson, WI). Peak bone mass at hip and spine for measurement on Lunar machines is taken as the mean BMD between age 20 and 40 yr, but this age range varies with DXA machine manufacture. Source of Fig. - Reference [29]

In AIDS, the mainly suggested risk factors for the development of osteopoenia and osteoporosis are the use of protease inhibitors, longer duration of HIV infection, high viral load, high lactate levels, low bicarbonate levels, raised alkaline phosphatase level, and lower body weight before antiretroviral therapy. There have also been a few case reports of pathologic fractures in AIDS patients with antiretroviral therapy-induced osteopenia and osteoporosis. The underlying mechanism triggering bone loss in HIV infected patients is still unknown [3].

3. BONE TURNOVER

A. BONE REMODELING

Growth in bone size and strength occurs during childhood, but bone accumulation is not completed until the cessation of linear growth (till the third decade of life). Even after bone accumulation has ended, there is a constant state of remodeling with repeated cycles of resorption followed by the deposition of new bone [3].

The cellular process of bone activity by which both cortical and cancellous bone is maintained is referred to as bone remodeling. This bone remodeling process takes place in discrete packets known as multicellular units [45]. Initially, a cell from the hematopoietic granulocyte-macrophage colony-forming unit lineage (along a bone surface) is activated and proliferates or transforms into an osteoclast [46]. An osteoclast creates bone cavity and subsequently, osteoblasts, derived from pleuripotent mesenchymal stem cells of the bone marrow, fill in the area of resorption with type 1 collagen [47]. Type I collagen ultimately becomes mineralized, probably as a function of the osteoblasts, thereby completing the process of new bone formation. There is an interdependency of the osteoclastic and osteoblastic activities where by osteoclasts are initially recruited to a particular site on the bone surface, and when their task is completed, they signal the osteoblasts to attend to that same site. This

interrelationship is known as coupling and is crucial link in the chain of bone-remodelling events [48]. A situation that interferes with coupling process or that causes imbalances between bone forming and resorbing relationship leads to significant loss of bone over the time.

Regulation of the bone-remodeling process is complex. Undoubtedly, there are numerous systemic hormones, such as parathyroid hormone, 1, 2 5-dihydroxy-vitamin D (calcitriol), calcitonin, estrogens, and androgens that regulate the process. Vitamin D is recognized as a stimulator of osteoclastic formation and a promoter of osteoblast differentiation [49]. There are also numerous local factors that play an important role in the physiology of bone remodeling like interleukins (IL-1 and IL-6), transforming growth factors (TGF), prostaglandins, tumor necrosis factor (TNF), lymphotoxin, colony stimulating factors (CSF), and gamma interferons [50-53].

OPG/RANKL/RANK system is the dominant, final mediator of osteoclastogenesis. This system explains the precise mechanisms by which preosteoblastic stromal cells control the osteoclast development. It is a specific factor produced by preosteoblastic/stromal cells that is both necessary and sufficient for osteoclast development. Osteoprotegerin (OPG) is a secreted soluble member of the tumor necrosis factor receptor superfamily (TNFR), also known as osteoclastogenesis inhibitory factor (OCIF) [54,55]. It has specificity for OPG/OCIF function for inhibiting osteoclast differentiation. The initial cloning and characterization of OPG as a soluble, decoy receptor belonging to the TNF receptor superfamily is the first step that eventually led to an unraveling of this system. Soon thereafter, the molecule blocked by OPG, initially called OPG-ligand/osteoclast differentiating factor (ODF). RANKL, is the key mediator of osteoclastogenesis in both a membrane-bound form expressed on preosteoblastic/stromal cells as well as a soluble form. RANKL, in turn, binds to its receptor, RANK, on osteoclast lineage cells. The decisive role played by these factors in regulating bone metabolism was demonstrated by the findings of extremes of skeletal phenotypes (osteoporosis *vs.* osteopetrosis) in mice with altered expression of these molecules. Identifying the factors regulating this system, the signaling mechanisms involved in the RANKL/ RANK pathway, and finally, potential alterations in this system in metabolic bone disorders that develop during HIV infections are crucial in understanding the mechanism underlying osteoclastogenesis in this particular type [56].

B. INTERACTIONS BETWEEN SKELETAL , IMMUNE AND HORMONAL SYSTEMS

The entry of HIV-1 into target cells requires the binding of the viral envelope glycoprotein (Env) with the target cell CD4 and an additional target cell co-receptor [57]. The co-receptors required for the fusion of the T cell-tropic and macrophage-tropic viruses with their target cells have now been identified to be fusin and CCR-5, respectively [58,59]. Fusin is a 7 TM domain protein with significant amino acid sequence homology to the IL-8 receptors. A CXC chemokine, PBSF/SDF-1, has recently been identified to be a ligand for fusin [60,61] The identification of CCR-5 as the co-receptor for macrophage-tropic viruses is consistent with an earlier report identifying the CCR-5 ligands (RANTES, MIP-1α and MIP-1β) as the major HIV suppressive factors produced by CD8$^+$ T cells for macrophage-tropic, but not T cell tropic, HIV isolates [62]. Besides fusin and CCR-5, use of other chemokine receptors such as CCR-2B and CCR-3 by a minority of HIV isolates has also been reported [63].

The hypothesis that the systemic activation of T cells in vivo leads to an osteoprotegerin ligand-mediated increase in osteoclastogenesis and bone loss [64]. This explains the interaction of HIV infection and bone mineralization. When the homeostasis between RANK/RANKL- osteoprotegerin is lost, there is an increased incidence of loss of bone mineral density. Interactions between cells of skeletal and immune system are important for the maintenance of bone homeostasis [65]. These cellular circuits are in part mediated by specific cytokines and changes in levels of these mediations may result in altered bone remodeling and disease [65-67]. Cytokines such as IL-1, IL-6, IL-11 and TNF-α may stimulate osteoclast activity [66-68] and enhanced IL-6 levels appear to play a pathogenic role in the enhanced bone resorption of post menopasual osteoporosis [69]. Some of these cytokines may also inhibit bone formation exerted by their negative regulatory effects on osteoblasts [65, 70,71]. This inhibitory effect on osteoblats combined with stimulation of osteoclasts suggest a pathogenic role for these cytokines in bone disorders characterized by increased resorption combined with decreased formation of bone [65].

Persistent activation of proinflamatory cytokines such as IL-1 and in particular TNF- α appears to play an important pathogenic role in HIV [72-75]. This proinflamatory activation may enhance HIV

replication, contributing to the development of immunodeficiency and certain clinical manifestations [74,75] and also be related to the endocrine abnormalities seen in HIV infected individuals [76,77]. Vitamin D metabolites and elements like Calcium, Magnesium, Phosphorus have complex effects in the bone system, with stimulatory effects on both formation and resorption [65,78].

Estrogen deficiency causes an increase in osteoclastic resorbing capacity [79-81]. Estrogen deficiency both directly and indirectly decreases the efficiency of intestinal and renal calcium absorption and reabsorption respectively. Testosterone deficiency in men is the major identifiable cause of male osteoporosis. It has analogous mineral metabolism effects. Evidence in support of gonadal hormone deficiency as the cause of increasing bone resorption is that specific receptors for estrogen and testosterone have been identified on the surface of the bone cells [82].

4. BONE MINERAL DENSITY IN HIV INFECTIONS

Bone mineral density is widely accepted as a measure of bone strength. BMD measurements have been shown to correlate strongly with the load bearing capacity of the hip and spine and with the risk of fracture. In patients with osteoporosis, there is a four fold to five fold increase in risk for fracture. And for patients with osteoporosis and a history of fracture, the risk of another fracture occurring is increased twenty fold.

While decreased BMD is certainly an important prediction of fracture risk, it is not the only parameter to consider. Fracture risk is also associated with a history of falls, low physical function such as slow gait speed and decreased quadriceps, impaired cognition and vision, and the presence of environmental hazards [3].

A. BMD in HIV infected individuals prior to use of Highly Active Anti Retroviral Therapy (HAART)

Prior to the widespread use of HAART, studies indicated that bone metabolism was altered, albeit minimally, in HIV infected individuals. Before the availability of protease inhibitors (PIs), low BMD was rarely observed in HIV infected individuals. However, the role of HAART in the reduction of BMD is controversially reported. According to some reports the direct correlation between the use of PI and osteoporosis is not so evident. BMD was significantly lower in HIV-seropositive patients in comparison with controls in lumbar spine, proximal femur and total body, without significant differences among treatment-naive patients and either of the treatment groups. Only time with HIV infection and not specific therapy was associated with BMD decreases [83] patients not receiving antiretrovirals also have a higher than expected prevalence of reduced BMD, which suggests that HIV itself may be a contributing factor, mediated by immune activation and cytokines [84]

In one analysis, 45 HIV-infected patients had statistically significant lower lumbar spine BMD scores than did HIV-negative controls. The subjects and controls did not differ in total or hip BMD. A small decrease in total body BMD was observed in a longitudinal follow up after 15 months. No significant reduction was found in spine and hip BMD. This matched the lines of osteopenia rather than osteoporosis [85]. But advanced stages of HIV infection demonstrated lower BMD of the individuals than HIV-negative controls. Several additional studies suggest a significant prevalence of low BMD in HAART-naive patients. This shows the probable role of HIV infection itself in decreasing BMD. The prevalence of osteoporosis in HAART-naive population is found to be approximately 28%, compared with the expected 16% in the general population [86-88]

Studies associated with biochemical markers of bone metabolism and bone biopsy of therapy-naïve HIV-infected individuals show a significant decrease in osteocalcin, a marker of bone formation and a marked increase in C-telopeptide, a marker of bone resorption in a comparison with healthy HIV-seronegative controls. These facts correlate with enhanced activation of the tumor necrosis factor system and increasing severity of HIV disease [89-91]. Numerous cytokines are known to induce differentiation of bone marrow precursors into osteoclasts. Hence bone resorption and osteoporosis are probably favoured. Abnormal immune system activation may be one of the probable causes that lead to bone resorption.

A study of bone samples from anti-retroviral therapy-naïve HIV infected subjects compared with healthy controls showed only decreased levels of osteocalcin in individuals with lower CD4 counts. No alterations in BMD or biochemical differences in bone metabolism were demonstrated [92].

B. BMD in HIV infected individuals after the use of HAART

A cross-sectional analysis of whole body, lumbar spine and proximal femur BMD in male subjects receiving HAART that included a protease inhibitor (PI), HIV-infected patients not receiving a PI and healthy seronegative adults using dual x-ray absorptiometry (DXA) scans was performed. Men receiving PI had lower lumbar spine BMD compared with the other two groups. 50% of the subjects on PIs were classified as osteopenic or osteoporotic according to WHO classification [13]. An assessment of bone metabolism in HIV infected subjects receiving HAART with 2 nucleosides and a PI [93] showed 43% of the subjects to be osteopenic or osteoporotic according to the WHO definition. Increased markers of bone resorption and bone formation, including elevations in urine pyridinolines, bone alkaline phosphatase, and osteocalcin. Another study in HIV-infected children also demonstrated HAART-associated losses in BMD that were associated with an increased rate of bone turnover [94]. Other studies have shown a more accelerated loss of BMD in individuals receiving potent antiretroviral therapy, but the association with PI use remains speculative and needs to be confirmed [14-15].

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. Prospective and longitudinal studies are necessary to determine the exact nature and mechanism of each individual factor in the pathogenesis of HIV-related bone mineral loss.

5. ASSESSMENT OF BONE REMODELING

Bone remodeling can be assessed using surrogate markers of bone turnover in the blood or urine. These markers include bone-specific alkaline phosphatase and osteocalcin, which are indices of bone formation. There are also urinary levels of pyridinolines and deoxypyridinolines and serum and urine levels of type 1 collagen telopeptides (CTX and NTX), which are indices of bone resorption. The level of these markers may identify changes in bone remodeling within a relatively short time - several days to months - before changes in bone density can be detected. It is important to realize, however, that marker levels cannot predict fracture risk and are only weakly associated with changes in bone mass. Therefore, they are of limited utility in the clinical evaluation of individual parametres [3].

6. CLINICAL MANAGEMENT

Current diagnosis and treatment of osteoporosis is primarily based on recommendations used for the management of disease in HIV-seronegative adults. Measurement of BMD as a routine test in HIV-infected patients is not recommended. However, plain radiographs and magnetic resonance imaging are the cornerstones of diagnosis. A detailed history of the past, physical examination, evaluation of nutritional status and potential secondary causes of osteoporosis are to be taken into consideration before the onset of the treatment of HIV-infected patients. Abnormal laboratory values of elevated alkaline phosphatase or low testosterone obtained during the course of HIV treatment should not be ignored during treatment [94]. The primary diagnosis of osteoporosis is 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 techniques are compared [95-97] Techniques for determining bone mineral density at various sites are summarized in Table 2. DXA studies are also useful to define fracture risk as well as to measure the efectiveness of various therapies on bone mass. Biochemical markers of bone turnover can provide complemetnary information to DXA scans, including changes in bone remodeling that can be identified before changes in BMD [1]. However the exact effectiveness of such markers remains controversial.

Table 2: Techniques for determining bone mineral density at various sites

Technique	Sites
Central dual-energy x-ray absorptiometry	Spine, hip, whole body
Peripheral dual-energy x-ray absorptiometry	Middle finger, wrist, heel, forearm
Single-energy x-ray absorptiometry	Forearm, heel
Quantitative computed tomography	Trabecular bone only; vertebral body

Peripheral quantitative computed tomography	Forearm
Ultrasound	Heel, patella, ankle

Management is dependent on the stage of bone disease and ranges from observation to total joint arthroplasty. Clinicians may help to prevent HIV-associated osteonecrosis by encouraging patients to limit their exposure to the established risk factors for the disease [98]. The treatment strategies that are effective in the general population should be pursued. Reversible causes of secondary osteoporosis should be studied. Vitamin D and calcium intake should be optimized. 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. Moderate physical activity is also recommended. The treatment for such conditions usually follows the general lines of management of osteoporosis [1].

Patients undergoing long-term corticosteroid treatment should begin primary prevention measures as soon as such agents are prescribed. Attempts to preserve bone should not be delayed until the underlying disease process is under way. Any patient taking glucocorticoids who has a T score of less than -1.0 should immediately be given pharmacologic treatment [99]. The most commonly used pharmacologic treatments for osteoporosis (excluding calcium and vitamin D supplements) are antiresorptive agents (estrogen, bisphosphonates, calcitonins, and selective estrogen receptor modulators). Other agents under development or already in use outside the United States include fluoride salts, parathyroid hormone, active forms of vitamin D (calcitriol, alfacalcidol), and anabolic steroids.

HRT

The utility of HRT (estrogen) for prevention of bone loss in early menopause is well established. HRT that is started at menopause retards or prevents bone loss and increases BMD somewhat. HRT continues to prevent bone loss for as long as it is taken, but bone loss resumes when estrogen is discontinued [100,101]. HRT is also effective in older women with established osteoporosis. Added potential benefits of HRT include controlling menopausal symptoms and reducing the risk of heart disease. Despite its documented benefits, however, some women find that the side-effect profile of HRT (eg, breast tenderness, abnormal uterine bleeding, endometrial hyperplasia, migraine, deep venous thrombosis) is unacceptable. Additionally, women may fear the relationship between HRT and breast cancer. Nevertheless, hormone replacement is considered first-line therapy in most postmenopausal patients.

Bisphosphonates

Candidates for bisphosphonate treatment include premenopausal women at increased risk for osteoporosis, postmenopausal women who forgo HRT, men with osteoporosis [102,103], and all individuals receiving high-dose corticosteroid therapy. In controlled clinical trials [104,105], bisphosphonates reduced the risk of fractures of the spine, hip, and wrist by 40% to 50% in postmenopausal women. These data are particularly significant because no randomized clinical trials have actually measured the effect of HRT on hip fracture, the most serious consequence of osteoporosis, even though observed studies consistently show that postmenopausal women who have been receiving HRT for 5 to 10 years have a lower risk of hip fracture than their counterparts who have not [106]

Several studies have shown bisphosphonates to be highly effective for prevention of glucocorticoid-induced bone loss, and these drugs have been approved by the US Food and Drug

Administration (FDA) for this indication. Risedronate sodium (Actonel), a pyridinyl bisphosphonate with FDA approval for the treatment of Paget's disease of bone, has recently been approved for prevention and treatment of postmenopausal and glucocorticoid-induced osteoporosis. Recent data from two controlled studies showed that this agent reduced the incidence of vertebral fractures by 70% in patients beginning corticosteroid therapy (when bone loss is most rapid) compared with controls [107].

Clinical experience with bisphosphonates has shown that patients may experience upper gastrointestinal disturbance, particularly esophageal symptoms (heartburn, painful or difficult swallowing) .Alendronate sodium (Fosamax) should be taken with 6 to 8 oz of plain water at least one-

half hour before the first food, beverage, or medication of the day. Other beverages (including mineral water), food, and other medications can reduce the absorption of oral bisphosphonates. Also, patients should not lie down until at least 30 minutes after taking alendronate and until after the first food of the day [108]. Clinical trials of risedronate have included postmenopausal women with ongoing gastrointestinal disease and those using aspirin or nonsteroidal anti-inflammatory drugs. Preliminary results [109] indicate that the incidence and severity of gastrointestinal events with use of risedronate are similar to those reported in the control group. Alternative dosage formulation and administration of bisphosphonates is under investigation.

Calcitonins

For patients who are unable or choose not to undergo HRT or take a bisphosphonate, a calcitonin is a viable alternative. Calcitonin-salmon is administered as a nasal spray (Miacalcin) or by injection. Calcitonin prevents bone loss and fracture in established osteoporosis, although it is somewhat less effective than HRT and bisphosphonates [110]. Recent results of a large controlled study (Prevent Recurrence of Osteoporotic Fracture) showed that calcitonin-salmon nasal spray reduced the incidence of new spinal fractures by 36% over a 5-year period, compared with placebo, in postmenopausal women who had previously experienced fracture. To date, calcitonin has shown no effect on nonvertebral fractures, and it has not been shown to reduce fracture risk in corticosteroid-treated patients [111]. However, calcitonin has modest analgesic properties, which may decrease opioid use and allow earlier ambulation in patients with acute vertebral fractures.

Selective estrogen receptor modulators

A selective estrogen receptor modulator may serve as an alternative to HRT for selected patients. Raloxifene (Evista) is the most studied of these drugs to date; its estrogenlike effects increase BMD . Raloxifene decreases total and low-density lipoprotein cholesterol levels, but unlike HRT, it does not affect high-density lipoprotein cholesterol. Also, unlike HRT, raloxifene does not appear to stimulate the endometrium . Recent data from the multiple outcomes of Raloxifene evaluation showed that 60- and 120-mg daily doses of raloxifene significantly decreased vertebral fracture risk during the first 36 months of treatment, compared with placebo. All patients also received calcium and cholecalciferol. At 36 months, raloxifene did not significantly lower the risk of nonvertebral fractures compared with placebo, although the cumulative incidence of nonvertebral fractures in active and placebo groups begins to diverge at 2 years. The effect of raloxifene on hip fracture is under investigation [112,113]. Specific studies with HIV-infected individuals should be conducted to determine the most effective way of this treatment.

7. CONCLUSION

Osteoporosis has been the recently recognized complication affecting HIV-positive patients. Etiology and pathogenesis of osteoporosis in HIV infection are still uncertain. Progression in HIV infection and HAART with PI are the possible factors that precipitate osteoporosis in HIV–sero-positive patients. Further studies should be extended to look into the natural history of bone loss during HIV disease. This would help to understand the mechanisms of uncoupled bone turnover and effects of PI therapy on HIV infected patients. As the number and life expectancy of HIV-positive patients treated with HAART increases, the development and treatment of osteoporosis in HIV infection should be taken into consideration in the long term management of HIV disease.

Conflict of interest

The authors have declared that no conflict of interest exists.

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