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More than Osteoporosis: Age-Specific Issues in Bone Health

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Abstract

Purpose of Review—The interaction between fall and fracture risk factors is an area of increasing clinical relevance, but little is known about the age-specific issues in bone health unique to HIV-infected adults. This review will focus on what is known about falls and fall risk factors among HIV-infected adults, and then review the association between decreased muscle, increased adiposity, and frailty with both low BMD and falls

Recent Findings—The rate of falls among middle-aged HIV-infected adults is similar to that of HIV-uninfected adults 65 years and older. Many of the clinical factors that contribute to low BMD overlap with risk factors for falls, resulting in a high risk of a serious fall among older adults with the greatest risk for a fracture. Low muscle mass, increased adiposity and metabolic syndrome, physical function impairment and frailty, common among older HIV-infected adults, contribute to an increased risk for low BMD and falls, and subsequently, may increase the risk of fracture among HIV-infected older adults.

Summary—Interventions with dual benefit on reducing fall risk and improving BMD are likely to have the greatest impact on fracture prevention in the older, HIV-infected adult.

Keywords

Osteoporosis; sarcopenia; obesity; frailty; falls; fracture

Introduction

Clinical Vignette

A 65 year old HIV-infected man was evaluated in the HIV clinic for a routine follow-up visit. He was diagnosed with HIV and cryptococcal encephalitis in 1989. His CD4 nadir was 21 cells/μL, and most recent CD4 lymphocyte count was 585 cells/μL. His HIV-1 viral load was suppressed on lamivudine, maraviroc, and boosted atazanavir. Comorbid illnesses included type 2 diabetes mellitus, hypertension, and benign prostatic hyperplasia;

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Conflicts of Interest:
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medications included metformin, lisinopril, tamsulosin, aspirin, pravastatin, and vitamin D. On further questioning, the patient reported 3 falls during the prior month. On examination, he exhibited orthostatic hypotension, his waist circumference was 102 cm, his body mass index (BMI) was 26.3 kg/m^2 but arms and legs were notably thin, and he had difficulty rising from a chair without use of his arms. A dual-energy x-ray absorptiometry (DEXA) scan was notable for a lumbar T-score −2.5 and femoral neck T-score −1.8; risk for a major osteoporotic fracture risk within 10 years was 7% using the FRAX algorithm [1]. *What unique issues should be addressed when evaluating the older adult with osteoporosis?*

Decreased muscle, increased adiposity, and frailty are integrally related to bone mineral density (BMD). However, the clinical consequence of low BMD is the fracture that results following a fall. Thus, rather than focus on low BMD, this review will first review what is known about falls and fall risk factors among HIV-infected adults, and then describe the associations between decreased muscle, increased adiposity, and frailty with both low BMD and falls. Due to the increasing age and comorbidity burden of treated HIV patients, research is commonly focused on the interactions between HIV, antiretroviral therapy (ART), and low BMD. Indeed, PubMed includes over 4000 publication citations in reference to “HIV and bone”. In contrast, the risk of falls in HIV has been minimally described. As of Janauary 25, 2016 only 12 PubMed citations included “HIV and ‘accidental falls’ ” and 3 of these reported rates of falls or characteristics of HIV-infected fallers [2–4]. As the proportion of HIV-infected adults aged 50 or older is projected to reach nearly 70% by 2030 [5], the interaction between falls and fracture risks is an area of increasing clinical relevance. Little is known, however, about the issues unique to HIV-infected adults.

Falls and Fall Risk Factors in HIV

A “fall” is most often defined as “an unexpected event in which the participant comes to rest on the ground, floor, or lower level”[6]. In the clinical setting, falls are most commonly assessed by retrospective self-report which may underestimate the actual number of falls, particularly if a fall is non-injurious [7, 8]. An individual’s own assessment of his or her risk of falling using tools such as the Activities Specific Balance Confidence [9] or Falls Efficacy Scale [10] is also highly predictive of falls [11]. Objective, standardized tests including the timed-up-and go (TUG) test, a 10-time chair rise test, or tandem stand can identify patients with balance or mobility problems suggestive of high fall risk [12, 13].

Self-reported falls were described among 359 middle-aged, HIV-infected adults on effective ART in a Colorado cohort; 30% sustained at least 1 fall during the prior year, similar to fall rates reported among HIV-uninfected adults aged 65 or older [3]. In a similar cross-sectional analysis from the University of California San Francisco SCOPE cohort, 26% of 155 HIV-infected adults (94% male) aged 50 or older on ART reported at least 1 fall in the prior year [2]. To further explore the effect of HIV serostatus on fall risk, falls were compared between HIV-infected and HIV-uninfected men and women in the Multicenter AIDS Cohort (MACS) and the Women’s Interagency HIV Study (WIHS)[14]. In these cohorts, no significant differences were found by HIV status in falls described retrospectively (24% HIV-infected versus 18% of HIV-uninfected participants reported at least 1 fall in the prior year, p=0.27). The lack of falls risk attributable to HIV may reflect that the HIV-infected and uninfected

MACS and WIHS participants are demographically similar in regards to overall burden of fall risk factors, while comparisons to the general population data reported by the CDC reflects a different demographic. The lower fall rate compared to prior studies in HIV-infected adults may be explained in part by healthier individuals agreeing to participate in the study, compared to a routine clinical assessment in the Colorado and SCOPE Cohorts. To further understand fall prevalence and risk factors, standardized assessment of self-reported falls are now being captured across multiple cohorts.

Falls are a common geriatric syndrome, and are the consequence of multiple interrelated factors including comorbidities (arthritis, diabetes, pain, depression), physical impairments (vision, cognition, neuropathy, strength, gait), and polypharmacy (Figure) [15]. A high prevalence of comorbidities, physical impairments, and polypharmacy associated with falls are also seen among HIV-infected older adults [16]. Similarly, many of the clinical factors that contribute to low BMD overlap with risk factors for falls, resulting in a high risk of a serious fall among older adults with the greatest risk for a fracture. For example, use of antidepressants, sedatives, and opiates are established risk factors for low BMD and were some of the strongest predictors of falls in the Colorado cohort [3]. Similarly, a greater number of prescribed medications were associated with an increased risk of falling in both the Colorado and MACS/WIHS Cohorts [14, 17]. In contrast to the strong associations between HIV-specific factors and low BMD discussed in prior articles in this journal issue, HIV-related characteristics and substance abuse appear to have minimal effect on fall risk. Outside of increased fall risk with current tobacco use or prior didanosine [3], and decreased fall risk with current protease inhibitor use (MACS/WIHS cohort)[14], no association was found with other HIV-specific variables or with substance abuse-related factors (hepatitis C, alcohol use, current illicit drug use).

Sarcopenia as a Risk for Low BMD and Falls

In healthy adults, a decline in both muscle quality (function) and quantity (mass) begins in the fourth or fifth decade of life [18]. Without intervention or if hastened by concomitant disease, the decline in muscle may result in *sarcopenia*, a term which refers to the loss of muscle mass alone, but has been more recently defined as a condition consistenting of both impaired muscle function and low muscle mass. Although sarcopenia and osteoporosis are two distinct processes, there is increasing evidence of important interactions which significantly impact on fracture risk. Sarcopenia is independently associated with an increased risk of low BMD in both Caucasian and Asian middle-aged and elderly individuals [19, 20]. Sarcopenia contributes to the development of frailty which itself increases the risk of disability and falls in the elderly. Studies suggest that individuals with both sarcopenia and osteoporosis have more comorbidities, as well as impaired mobility, diminished quality of life [21], and an increased risk of falls [22]. New terminology including osteosarcopenia, sarco-osteoporosis, and musculoskeletal frailty highlight the integrated mechanisms of loss and similar risk factors underlying both disease processes [23].

The interconnectedness of bone and muscle are seen at several levels from direct muscle-bone interactions to shared pathways including endocrine influence, nutrition and lifestyle factors, demographics, and genetic features. Muscle and bone cells share a common

progenitor in the mesenchymal stem cell, and thus are susceptible to similar genetic or epigenetic influences [24]. Muscle and bone develop in parallel throughout adolescence, and decline similarly with older age. The mechanical loading force of muscle on bone is well-recognized: increasing levels of acute, dynamic stress creates greater muscle contractions, and stimulate cortical bone formation. In contrast, in situations of prolonged bedrest with very limited muscle contraction or among astronauts with zero gravity and no mechanical loading, marked losses in both BMD and muscle result [25, 26]. The molecular and cellular mechanisms that underlie the muscle-bone crosstalk and whether bone provides a similar stimulus to muscle are less understood research questions [27]. Endocrine pathways such as the growth hormone (GH)/insulin-like growth factor (IGF)- 1 axis are critical in the regulation of both muscle and bone growth [28]. Both the concentration and effectiveness of serum and bone IGF-1 decrease with age, and lower levels of IGF-1 are associated with a lower BMD [29–32]. Low IGF-1 or variations in the GH/IGF-1 gene have also been associated with low lean body mass (LBM) or impaired muscle function [33–36] and frailty [37, 38].

Sarcopenia has been evaluated in HIV in the absence of the AIDS wasting syndrome and malnutrition. Although some studies have suggested that the rate of lean muscle mass loss may not differ from that in the general population [39], low muscle mass is not uncommon, with 20–35% of HIV-infected participants meeting the DXA-defined criteria for low appendicular lean mass [40, 41]. As the FRAM study previously confirmed that both sarcopenia and visceral adiposity are independent predictors of mortality in treated HIV-infected persons [42], the potential for clinically important consequences of low LBM is evident. Furthermore, the impact of greater total body mass on BMD of HIV-infected persons is described in multiple cohorts [43–45]. The association between LBM, in particular, and bone density was first described early in the AIDS era [46]. Subsequent cross-sectional and longitudinal studies have corroborated these findings [47]. Among HIV-infected naïve participants initiating ART through the AIDS Clinical Trials Group Study 5224s, a greater increase in LBM after 96 weeks of ART was independently associated with greater week 96 increases in both hip and lumbar spine BMD [48]. Among participants with available follow-up DXA scans, low LBM was a significant predictor of subsequent decline in BMD over an average of 7 years of follow-up [49].

In addition to the decline in muscle mass and function, an increase in the amount of fat content within and surrounding skeletal muscle is seen with aging among HIV-uninfected populations [50]. The fatty infiltration of skeletal muscle, as defined by lower attenuation on computed tomography (CT), has been associated with fall and fracture risk beyond that predicted by muscle mass or low BMD. In the Health, Aging, and Body Composition (Health ABC) study of HIV-uninfected adults ≥ 70 years, low CT-attenuation of skeletal muscle was associated with increased risk of hip fracture independent of BMI, percentage body fat, age, height, race, gender, and bone mineral density. Furthermore, skeletal muscle fat infiltration was the only significant muscle parameter of fracture risk in models including muscle strength, physical performance score, and thigh muscle cross-sectional area [51]. Subsequent studies within the Health ABC Cohort and other cohorts have found similar, independent associations between skeletal muscle fat infiltration and fracture risk [52–54]. Although the mechanisms for this association have not been delineated, greater fatty muscle

infiltration may lead to weaker mechanical loading forces on bone, may be associated with poorer postural stability, or could increase local inflammation with a detrimental effect on bone resorption. In the MACS, middle-aged HIV-infected men had significantly greater fatty muscle infiltration of the mid-thigh musculature compared to uninfected men, and greater fat correlated with decreased grip strength. Furthermore, this measurement of muscle quality decreased with increasing age among the HIV-infected men, but not the uninfected men [55].

Obesity, Diabetes, and Metabolic Syndrome as Risk for Low BMD and Falls

Metabolic diseases, including type II diabetes mellitus, dyslipidemia, obesity, and the metabolic syndrome occur with increasing frequency among older adults. These disorders often occur together and may share underlying pathogenic features. The concept of an "allostatic load" suggests that the accumulated dysregulation across physiologic systems including chronic inflammation, cardiovascular disease, lipid and glucose disorders, is associated with decreased bone strength, despite the lack of an independent effect of each condition on BMD [56]. Although obesity is generally associated with greater BMD, the distribution of fat may be a better predictor of BMD and bone quality than the amount of total body fat described by the BMI alone. Indeed, some studies have demonstrated an increased hip BMD among both men and women with visceral obesity [57–59], while visceral obesity had either a weak or negative correlation with lumbar spine BMD [59–61]. Visceral adiposity has been negatively associated with bone density, strength, and structure in the majority of studies, presumably due in part to heightened inflammation and altered adipocyte-secreted or converted hormones [62]. Adipose tissue within the bone marrow also appears to be a strong predictor of low BMD [63]. Although diabetes does not appear to be associated with low BMD, an increased rate of bone loss [64] or abnormal micro- and macro-architecture of diabetic bone may explain the greater hip fracture risk among diabetics [65].

The relationship between obesity, diabetes, and metabolic syndrome with fall or fracture risk is more complex. Obesity has commonly been considered as protective against fractures [66, 67], due to the mechanical loading effects of increased body weight on BMD and the shock-absorption of additional adipose tissue, particularly over the greater trochanter [68]. In contrast, obese individuals may have greater postural and gait instability, predisposing to a higher fall risk [69]. Indeed, obesity is consistently associated with disability, impaired mobility, impaired physical performance, and frailty [70–72], which are themselves risk factors for falls. More recent studies have suggested that the relationship between obesity and fracture risk appear to differ between genders and across fracture site [73]. Comorbidities associated with obesity, including hypertension, inactivity, and neurocognitive disease add additional fall risk [74]. Type II diabetes mellitus may increase fall risk via peripheral neuropathy, visual impairment, and autonomic dysfunction. Similarly, metabolic syndrome has been associated with impaired exercise capacity [75] and may be an independent risk factor for falls [76].

Similar to HIV-uninfected populations, among HIV-infected participants, higher body weight has been a consistently protective factor for BMD [45, 77], while the effect of

visceral adiposity differs: in one cohort, both visceral adiposity and hyperglycemia were associated with low BMD [78]. Increased visceral fat over 96 weeks following ART initiation was associated with increased BMD at the hip but decreased BMD at the lumbar spine in the AIDS Clinical Trials Group study A5224s [48]. Similar to the effects on BMD, diabetes, but not obesity, was an independent contributor to recurrent falls in the Colorado Cohort [3]. In a separate cohort, abdominal obesity was strongly associated with frailty, and thus could subsequently increase the risk of falls [79]. Changes in body fat including both peripheral lipoatrophy and central lipohypertrophy contribute to reduced hand grip strength [80], a risk factor for falls.

Frailty and Physical Function Impairment as Risks for Low BMD and Falls

Frailty is a geriatric syndrome often overlapping with obesity and/or sarcopenia, and is characterized by decreased physiologic reserve. Several diagnostic criteria are used to define frailty clinically. Regardless of the definition, frailty is considered the end result of multiple potential insults including alterations in hormones (growth hormone, estrogen, testosterone), heightened inflammation, low physical activity, and poor or under-nutrition. These alterations are associated with the clinical manifestations of slowness, weakness, and fatigue. Thus, many of the risk factors for frailty overlap with the risks for low BMD, sarcopenia, and falls, which may subsequently result in fractures. Not surprisingly, frailty and other impairments in physical function such as balance impairment, slow gait speed, or weakness, are also strong predictors of both falls and fractures in cohorts of older, HIV-uninfected adults [81–86]. The association between frailty and low BMD in HIV- uninfected populations is not well-established and may depend on the definition of frailty used and the prevalence of osteoporosis in the population under investigation [87–91]. Most existing data is cross-sectional but a recent study of older women found that while baseline osteoporosis was not associated with frailty, frail participants were more likely to develop osteoporosis in follow-up [87].

Relatively little is known about the relationships between frailty or physical function impairment and falls, low BMD, and fracture among HIV-infected older adults, outside of the studies previously mentioned. Recent evidence suggests that impaired locomotor function, as determined by routine functional tests of the lower extremities, is both common and increases over time in older HIV patients with comorbidities [92, 93]. This is an important risk for falls and interacts closely with the decline in gait speed which also occurs in older HIV patients [94]. In the Colorado cohort, nearly 70% of HIV-infected participants with functional impairment or frailty also had osteopenia or osteoporosis at the hip or lumbar spine compared to <40% of participants in the high-function group [41]. Furthermore, the frailty components of exhaustion and unintentional weight loss, as well as objective difficulty with balance were all significantly associated with a greater odds of falling [3]. In the MACS/WIHS cohort, the presence of imbalance symptoms was one of the strongest predictors of falls, even after adjusting for comorbidities, polypharmacy, and HIV-related characteristics [14]. In a subsequent Multicenter AIDS Cohort Study, Brown, et al found that lower self-reported balance confidence was a significantly better predictor of falls than objective tests of strength or balance [95]. As all these studies are observational, the cause and effect relationships cannot be determined. Persons with frailty or impaired

physical function are less likely or less able to engage in more strenuous regular physical activity. The resultant decline in muscle mass from physical inactivity may amplify the fall risk and BMD decline. Furthermore, chronic pain, fatigue, and altered sleep are additional risks for falls. These conditions occur commonly in HIV patients, and are known risk factors for polypharmacy, but are infrequently considered in routine care settings [96–99].

Testosterone and Vitamin D on Falls and Fracture Risk

Testosterone decreases with age and is a known risk factor for both sarcopenia and visceral adiposity [100]. The potential contribution of hypogonadism to risk of falls remains uncertain. This relates partly to the study design limitations related to whether the condition is defined on the basis of total, free or bioavailable testosterone. Although hypogonadism may contribute to frailty via its effect on sarcopenia, the evidence is unclear whether this refers to frailty as defined by the frailty phenotype or only to some of its components [101, 102]. This distinction is of more than academic interest, as numerous interventional studies in hypogonadal patients have not clarified whether the clinical manifestations of hypogondism presumed to be related to physical function in the elderly can be improved with judicious use of function promoting anabolic therapies [103]. In HIV, hypogonadism is more pronounced in both untreated and effectively treated patients compared to HIV-uninfected men [104–106].

Vitamin D plays an important role in bone health and physical performance [107] possibly via effects on muscle function and strength [108, 109]. Vitamin D deficiency is as common in HIV, as it is in the general community and is of multifactorial etiology [110]. Although some studies suggest that the widespread adoption of universal vitamin D supplementation will prevent falls in the general elderly population, careful meta-analyses do not support this recommendation [111]. Similarly, although studies show an association between vitamin D deficiency and frailty, evidence for a causal effect and whether supplementation can prevent its occurrence are lacking [112]. Furthermore, two recent studies suggest that vitamin D supplementaion may increase the risk of falls or functional decline [113, 114]. Among HIV-infected persons initiating ART with efavirenz/emtricitabine/tenofovir disoproxil fumarate, high dose vitamin D3 (4000 IU/day) and calcium supplementation significantly attenuated BMD losses [115], suggesting a beneficial effect on fracture risk reduction. No association between 25-hydroxy vitamin D levels and physical function/frailty was found in the Colorado cohort [41], but whether high dose vitamin D supplementation could attenuate fall risk, decrease frailty, and improve muscle function in HIV is unknown.

Clinical Vignette Continued…

In discussion of the risks and benefits of therapy with the patient, he and his provider changed his tamsulosin to finasteride to decrease his orthostatic hypotension. Testosterone levels were low-normal, but therapy was held due to his additional cardiac risk factors. Vitamin D supplementation was continued but increased to 2000 IU daily, calcium supplementation was initiated, and bisphosphonate therapy was held. Occupational therapy completed a home safety evaluation to reduce extrinsic fall risks (i.e., loose rugs, cords, low lighting). The patient began physical therapy for balance and resistance training, followed by

a regular indoor walking regimen and weekly tai chi. He had only 1 fall during the subsequent year, his lumbar T-score improved to −2.0, and femoral to −1.6.

Conclusions

The combination of increased fall risk and lower BMD highlights the importance of evaluating, monitoring, and modifying risks for both falls and fracture. In the context of the aging HIV population, we have expanded the perspective of low BMD as a diagnosis or surrogate of a specific organ disease, to that of falls as a geriatric syndrome. Considering falls as a geriatric syndrome allows for a broader, multifactorial approach. Although no data exists on specific fall or fracture prevention in HIV-infected populations, successes with other populations or other treatment outcomes can be extrapolated to develop falls prevention guidelines for the clinical or research setting. The evaluation, prevention, and treatment of falls and fractures in the older, HIV-infected adult should be multifactorial and encompass the medical, social, and psychological aspects. Brief standardized assessments for falls, fear of falling, and/or fall risk factors should be incorporated into the routine clinical assessment. Ideally, those at risk of falling can be identified before a fall, and the particular risk profile minimized. Among other benefits, this will serve to less the fear of falling that may subsequently limit activities. Low BMD is one of many risk factors for fracture, and should be evaluated together with anthropometric changes, functional impairment, and environmental risks. Interventions with dual benefit on reducing fall risk and improving BMD are likely to have the greatest impact on fracture prevention in the older, HIV-infected adult.

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Bullet Points

- The interaction between falls and fracture risks is an area of increasing clinical relevance, however little is known about the issues unique to HIV-infected adults.
- The combination of increased fall risk and lower bone mineral density highlights the importance of evaluating, monitoring, and modifying risks for both falls and fracture.
- Considering falls as a geriatric syndrome allows for a broader, multifactorial approach to prevention and treatment.
- Interventions with dual benefit on reducing fall risk and improving BMD are likely to have the greatest impact on fracture prevention in the older, HIV-infected adult.

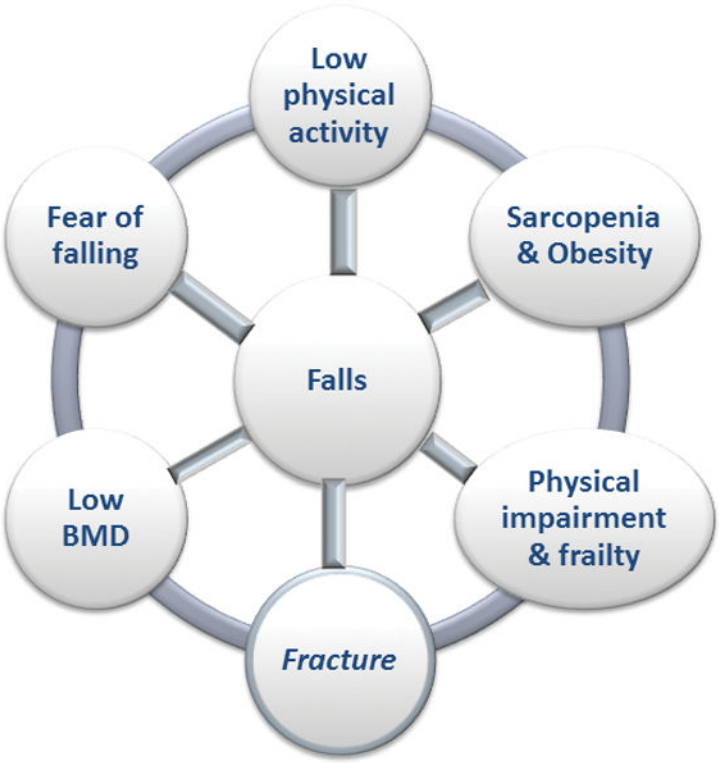

Figure. The interrelated factors contributing to falls and fractures

Falls are multifactorial, and affected by adiposity, sarcopenia, physical function impairment, and low physical activity; a fall can also result in many of these same factors, leading to further physical function impairment, fear of falling, and subsequent fracture.