EDITORIAL

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HIV and Bone Health: Considerations for Menopausal Women Living with HIV in Sub-Saharan Africa

Musculoskeletal (MSK) conditions are among the most common health problems in older age. As life expectancy rises in sub-Saharan Africa (SSA), the number of older adults is expected to increase more rapidly than in any other part of the world. Globally, MSK diseases account for the greatest number of disability-adjusted life years lost,[1] a major contributor being the age-related decline in muscle and bone strength leading to osteoporosis, falls, and fractures with their associated morbidity, mortality, and economic burden. With the predicted older population explosion, Africa will have the highest proportional increase in fracture rates globally.[2] The high prevalence of human immunodeficiency virus (HIV) infection in this part of the world is relevant in this context because of its association with increased fracture risk.[3]

Many adults are living longer with HIV due to wider access to combination antiretroviral therapy (ART).[4] Unpublished data from HIV treatment programs in SSA show that between 20% and 50% of adults receiving HIV treatment are over 50 years of age [U.S President's Emergency Plan for AIDS Relief data, unpublished], and this proportion is expected to rise.[5] In SSA, 63% of new HIV infections occur in women and girls.[6] These epidemiologic trends suggest that many women currently living with HIV infection will live through menopause and experience its consequences, including the risk of osteoporosis and fragility fractures. Although data on fractures in Africa are scarce, findings from resource-rich settings consistently show that HIV infection is associated with low bone mineral density (BMD) and increased fracture risk.[7]

A number of factors have been implicated in the pathogenesis of HIV-associated bone loss, including ART. On ART initiation, there is a transient acceleration of bone turnover, resulting in bone loss[8]; annual rates of bone loss between 2% and 6% have been reported, although BMD generally stabilizes after 1 to 2 years. Bone loss associated with tenofovir disoproxil fumarate (TDF)-containing treatment regimens is greater compared to those not containing TDF, although whether this translates into increased fracture risk is uncertain. The pathophysiological mechanisms of TDF-related bone loss are not well understood but may include a direct toxic effect on bone cells, proximal renal tubular dysfunction, and parathyroid hormone-triggered increased bone resorption.[9]

Among older women, the transition through menopause is associated with accelerated bone loss related to the effect of estrogen deficiency on bone remodeling. There are few studies evaluating the prevalence of osteoporosis in Africa in menopausal women.[10] A recent prospective study describing MSK aging in 488 Gambian adults reported an annual BMD loss of 1.2% at the total hip in women after age 50 years.[11] A cross-sectional study using high-resolution quantitative QCT in perimenopausal women in South Africa suggested that women living with HIV had lower cortical density at the distal radius than their noninfected peers.[12] There are some reports on hip and vertebral fracture prevalence in southern Africa; in Botswana, the incidence of hip fractures is low, with estimated remaining lifetime risks of hip fracture in men and women over 50 years of age of 1.4% and 1.1%, respectively, while in South Africa a study of hip fractures among the different ethnic groups confirmed a lower incidence rate in black African women (43.6 per 100,000) than white women (176.0 per 100,000). A similar pattern was seen in men but at a lower rate.[13,14] A cross-sectional analysis in rural South Africa showed that osteoporosis was common in individuals over 50 years and HIV was strongly associated with osteoporosis: 37% of women with HIV had femoral neck osteoporosis compared to 15.7% of those without HIV.[15] However, longitudinal data for rates of bone loss among menopausal women with HIV are lacking.

In this issue of the *Journal of Bone and Mineral Research*, Madanhire et al.[16] provide data on BMD changes during the menopausal transition in urban-dwelling South African women with and without HIV and investigate whether HIV infection modifies the effect of menopause on these changes. The authors conducted a 5-year population-based longitudinal study among 450 women aged 40 to 60 years in Soweto, South Africa. Of the 65 women who were living with HIV, the majority (81.5%) were receiving ART. All women were staged as pre-, peri- or postmenopausal at both baseline and the study end, and BMD was assessed by dual-energy X-ray absorptiometry (DXA) at the lumbar spine, total hip, and whole body. Interestingly, although at baseline 65% of women were obese, the overall prevalence of osteoporosis in those aged ≥ 50 years was 13.6% (25% of those with HIV). Significant bone loss at all sites was observed over the study period in women both with and without HIV, with the greatest losses occurring in those transitioning to menopause and those who were postmenopausal throughout. However, after adjustment for age,

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weight, weight change, and follow-up time, significantly greater bone loss at all sites was seen in women with HIV compared to those without. Over the study period, the losses in BMD observed in women with HIV amounted to 9% and 4.5% at the lumbar spine and total hip, respectively.

A consideration in the interpretation of the aforementioned findings is that most studies looking at population differences define osteoporosis using World Health Organization (WHO) T-score thresholds based on the National Health and Nutrition Examination Survey (NHANES) non-Hispanic white population. A growing body of evidence indicates that individual populations have very different reference values. In a study in Zimbabwe, for example, BMD values for black Zimbabwean women were closer to those of US white women than US black women when the NHANES data were used as a comparator.[17] Similarly, in our previous study comparing BMD among HIV untreated and HIV negative Ugandan women aged 18 to 35 years, analysis using NHANES reference ranges for white non-Hispanic women gave a higher prevalence of low BMD in the two groups of 20.6% (93/452) and 8.7% (6/69), respectively, than what would be expected in a white population of the same age.[18] The lack of a locally derived reference population could have led to underestimation of the association between HIV and bone loss in the current study. Importantly, while the majority of bone loss occurs in the first 1 to 2 years of ART, over 80% of the women in this study were already receiving ART (presumably TDF, lamivudine [3TC], and efavirenz [EFV], the first-line regimen in South Africa) for varying periods at the time of the study.

This is the first study to investigate the interaction between HIV and menopause on bone mass in SSA and provides novel insights into bone health among menopausal women living with HIV in resource-limited societies.

Further studies are needed to determine the impact of the increased rates of bone loss during menopause on fracture risk and the potential role of interventions to prevent menopausal bone loss. As suggested by the authors, their findings provide a rationale for routine bone health assessment in postmenopausal women living with HIV in South Africa. Although the use of DXA is limited by availability and cost,[19] ethnic-specific models of FRAX for South Africa are now available and can be used in HIV clinics to assess fracture probability in postmenopausal women.[20]

Disclosure

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