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INCREASED RISK OF FRACTURE ASSOCIATED WITH HIV AND KIDNEY DISEASE: A CASE REPORT

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ABSTRACT Patients with human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) have an increased risk of osteoporosis and fractures when compared with people of the same age and sex. As a result, the risk of osteoporosis and fractures of the vertebra, lumbar, and hip is higher in people living with HIV compared to the general population. This condition is magnified in the setting of renal failure with superimposed metabolic bone disease. Here, we present a case of fracture and osteoporosis in a patient with long-standing, well-controlled HIV with superimposed metabolic bone disease and kidney failure.

KEYWORDS : Fractures, HIV, Antiretroviral Therapy, Metabolic Bone Disease, Osteoporosis, Kidney Failure

INTRODUCTION

Thirty-nine million people are estimated to be positive for human immunodeficiency virus (HIV) infection globally, with more than 80% of them residing in the regions of Sub-Saharan Africa and Asia-Pacific [1]. In the United States, as of 2022, HIV seropositive prevalence sits at about 1.2 million, which is approximately 0.4% of the population (one person for every 250, or 1.2 million). Due to the various efficacious antiretroviral therapies (ART) available today, people diagnosed with acquired immune deficiency syndrome (AIDS) and HIV-positivity have a significantly improved lifespan. The life expectancy of people living with HIV is similar to that of the general population living without HIV/AIDS [2]. As a result, the focus on the management of HIV/AIDS patients has shifted to countering the effects of co-morbidities of aging.

However, despite the decline in mortality due to illness brought on by HIV, the last two decades have also seen a proportional increase in non-AIDS-defining illnesses (NADI). People living with HIV who have longer lives and extended exposure to ART are prone to develop NADIs that involve the kidneys [3]. As a result of an improved survival rate from HIV itself, the percentage of dialysis patients living with HIV has increased [4]. Kidney disease is a highly prevalent and persistent public health concern in the US. About 11% of the adult population (37 million) [5], of which the majority are over the age of 65, are diagnosed with chronic kidney disease (CKD). This already high prevalence may be an underestimate due to most CKD being diagnosed in advanced stages. Approximately 0.2% of the US population have end-stage renal disease (ESRD), requiring dialysis or transplant. Nearly 20% of CKD patients are identified as African Americans and are the largest patient group by demographic [6]. Consequently, black Americans are four times more likely to develop ESRD than white Americans [6].

People living with HIV carry a particular risk of developing kidney disease and a variety of co-morbidities that occur with aging, such as osteoporosis. Although the direct relation between HIV and bone loss is generally known to be confounded by numerous factors such as age, Body Mass Index (BMI), estrogen, physical fitness, and substance use, there is still a strong association between HIV infection and lower bone mineral density after adjusting for patient demographic [7].

The main significant risk factors of kidney disease include having a history or family history of diabetes, hypertension, heart disease, obesity, and being of black race [6]. The majority of HIV-associated nephropathy (HIVAN) focal sclerosing glomerular sclerosis and HIV immune kidney disease (HIVIKD) lupus-like glomerulonephritis have been historically described, particularly in black patients, especially before ARTs were available, and are associated with the APOL1 gene [8]. Additionally, some other risk factors for developing kidney disease in HIV-positive patients include Hepatitis C co-infection, low CD4 counts, and ARTs. Although ART has been indispensable for prolonging the life of HIV-positive patients, the usage of ART (most notably tenofovir) can impair kidney function.

Case Presentation

A sixty-year-old African American woman with a long history of HIV of over 22 years with an undetectable viral load and a normal CD4 count, diabetes, hypertension, and ESRD recently started on dialysis. She presented to the hospital after a fall and pain in her right arm. She has had a long history of orthopedic issues, starting ten years ago when she had a mechanical fall from standing and twisted and fractured her right femur. She had open reduction and internal fixation and, subsequently, due to prolonged non-healing, had placement of a rod. This required revision after several years due to the migration of the rod. She then had a second fall with a fracture of her right ulna that was complicated by delayed healing.

Three years ago, she was diagnosed with CKD stage two from hypertensive nephrosclerosis and recently started on dialysis after acute renal failure from interstitial nephritis secondary to a proton pump inhibitor.

Since starting on dialysis, her orthopedic issues have worsened with further migration of the rod, causing pain, a slight decrease in limb length, increased instability, and a mechanical fall from a misplaced step resulting in a fracture of her left ulna when she hit a desk. She was not found to have an acute fracture on exam and was sent home on this visit with a follow-up with endocrine to discuss medication and evaluation with a DEXA scan to treat and evaluate renal metabolic bone disease and osteoporosis from prolonged exposure to antiretroviral therapy.

DISCUSSION

HIV and Bone Fracture

It is generally observed that people living with HIV experience bone fracture ten years earlier than HIV-negative individuals. Not only does HIV-positive status positively correlate with osteoporotic status, but antiretroviral therapies (ART) have been implicated in further decreasing bone density among HIV-positive patients [9,10]. ART such as Tenofovir is associated with significant bone loss in individuals with HIV infection, resulting in osteopenia and osteoporosis typically within 6 months of treatment initiation. The clinical consequences of low bone mineral density are a great risk factor for fragility fractures and are more common in older HIV patients and those on ART. Frailty of bone in HIV patients has a 10% prevalence (about twice that of the general population), and the increased propensity of falls in older patients results in greater fracture prevalence, morbidity, and mortality [11].

An additional reason of bone deficit complications resulting from HIV infection is due to viral infections of osteoclast, the cells responsible for bone resorption [12]. This infection is primarily driven by the viral protein Nef [12,13]. Nef, which stands for "Negative Factor", plays a crucial role in disrupting normal osteoclast function, leading to an imbalance in bone remodeling and ultimately resulting in bone deficits. These deficits make individuals living with HIV more susceptible to fractures.

The Effect of Antiretroviral Therapies on the Bone

With the utilization of ART and remarkable advancements in the care of HIV patients, there has been a shift in the discussion of the causes of morbidity and mortality in people living with HIV. The focus has shifted from the traditionally HIV-associated disease to more chronic/age-related diseases that develop at a faster tempo compared to the HIV-negative population. The higher incidence of osteoporosis was initially documented in the early 2000s. This has been attributed to a combination of factors, including the direct constant immune activation created by sustained low-level viremia, which would persist despite the undetectable viral load, and the effect of ARTs on bone metabolism. Three mechanisms may explain the effect of ART on the bone: 1) osteoblast inhibition [14]; 2) functional vitamin D deficiency leading to hyperparathyroidism [15]; and 3) proximal tubule dysfunction in the kidney.

ART initiation has been associated with bone mineral density (BMD) loss across all classes of antiretroviral therapies (ARTs), peaking in bone loss within the first 24 months of treatment. Beyond the 24 months, the class of ART has been a differentiating factor in the rate of progression of BMD loss. Integrase inhibitors have demonstrated the most negligible effect on BMD loss, whereas protease inhibitors and nucleoside reverse transcriptase inhibitors (NRTIs), specifically Tenofovir Disoproxil Fumarate (TDF), have the worst impact on BMD loss.

Two and three-drug combination ART regimens continue to be the standard of care to achieve effective virologic suppression and prevent the development of drug resistance. Combining integrase inhibitors with non-NRTIs and using less toxic NRTIs, such as the newer Tenofovir Alafenamide (TAF) formulation, may effectively reduce long-term bone loss. However, the long-term effects of these drugs on BMD loss have yet to be validated in head-to-head trials, which are limited mainly by the cost of these medications.

The Effect of Viral Infection of Osteoclasts on the Bone

Viral infections of osteoclast cells can have a significant impact on bone health by disrupting the normal balance of bone resorption and formation. Specifically, Nef, the viral protein that is expressed by all primate lentiviruses, has been shown to alter osteoclast function. Nef can increase the activity of these bone-resorbing cells, leading to excessive bone degradation [12]. This imbalance favors bone loss and can result in pathological bone deficit conditions.

Nef is responsible for the activation of Src which is a regulatory factor of bone homeostasis by regulating the activity of podosomes, interconnected F-actin rich structures located on the external surface of the plasma membrane [12,13]. HIV, via Nef and its effect on podosomes, augments the osteolytic activity of bone resorption (Figure 1) known as the sealing zone (SZ) [13]. The SZ becomes larger due to F-actin enrichment and facilitates a larger resorptive zone where osteolytic enzymes are secreted, causing higher-than-normal bone resorption, increased risk of fracture, and accelerating osteoporosis and other bone disorders [12].

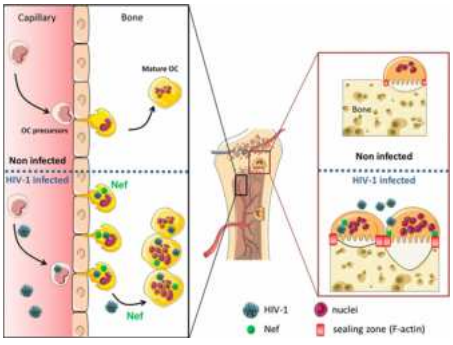

Figure 1: Graphic illustrating how HIV triggers bone deficits in HIV-infected patients. The graphic shows how viral protein Nef leads to an increase in osteoclast number and osteolytic activity leading to larger and denser sealing zones [12].

Bone Fracture in End Stage Renal Disease

Bone fracture in ESRD patients is a source of high morbidity, resulting in a significant decrease in the quality of life. Hip fracture rates in patients with ESRD are five-fold higher than in the general population [16] despite multiple advances in the treatment for mineral deficiency and bone diseases in dialysis patients. The incidence of hip and vertebral fractures has increased roughly 2-fold from 1992 to 2004 (12.5 to 25.3 fractures per 1000 patients) [17]. More recently, the fracture rates have improved in older patients, whereas the fracture rates of younger patients remain unchanged.

Patients 85 years of age or older have increased in these past decades, as did the burden of comorbidities with ESRD and hip fractures. Although hip fracture incidence rates in patients reaching ESRD are higher today than in 1992 [16], hip fracture rates have improved significantly more in older women than in older men. In patients without ESRD, the types and frequencies of hip fractures have been well characterized, and they have changed over the years, possibly due to public awareness and fall prevention programs aimed towards postmenopausal women, with wider use of calcium, vitamin D, and antiresorptive therapies [18]. On the other hand, ESRD-

specific hip fractures in patients on dialysis have been less characterized. The most common types of fractures reported in ESRD patients are femur neck (49.2%) and intertrochanteric fractures (44.2%).

Vertebral fractures in a Dutch study of ESRD patients had a high prevalence (34%) and incidence (29% after a median two-year follow-up) in a relatively younger population (mean age 52 years) of patients with ESRD. The vertebral fracture prevalence is remarkably higher compared with the general population of the same age, ranging between 2-11%. The data in the study showed no relationship between CT-measured-vertebral trabecular BMD versus vertebral fracture. The study also showed a U-shaped relationship of parathyroid hormone (PTH) for vertebral fracture [19].

Bone fracture in patients with chronic kidney disease leads to increased mortality, morbidity, and decreased quality of life. Furthermore, mortality associated with hip fractures doubles in patients on dialysis versus those who are not [20]. It is, therefore, essential to assess the risks for bone fractures in patients with ESRD. Kidney Disease Improving Global Outcomes (KDIGO), a global nonprofit organization that develops and implements evidence-based clinical practice guidelines in kidney disease, recommends closely observing serum PTH or alkaline phosphatase to assess for BMD and bone disease. In addition, bone biopsy is instrumental in characterizing renal osteodystrophy and guiding treatment [20,21].

Immune reconstitution and Dialysis

The number of patients with both HIV and ESRD who started dialysis peaked in 1997 at 27%, with 95% of those patients being Black or Hispanic. That rate quickly dropped with the use of ART in the early 2000s, with a steady rise in the number of ESRD patients with HIV. In fact, the incidence of major fractures has increased in both HIV patients and ESRD patients. A review of cross-sectional studies found that adults living with HIV had a 6.4-fold increased odds ratio of osteopenia and a 3.7-fold increase of osteoporosis compared to the HIV-negative population [10]. It has been observed that ART reduces the incidence of ESRD in Black patients [3]. However, Caucasian patients, who tend to have more fractures in both non-HIV and non-ESRD populations, have not been observed to have reduced fractures with ART. Furthermore, the incidence and effect of race have not been studied in people living with HIV on dialysis. With so many patients who have both HIV and ESRD rising, the question of the relative risk factor of both diseases on the bone as well as which factors in this population create the most risk has not been studied.

The effect of dialysis in patients receiving ART, and whether it affects the reconstituted immune cells, still needs to be understood in the context of bone metabolism. In addition to the well-explored etiologies of bone loss, such as hormonal deficiencies and chronic virus-driven immune activation, the consequences of immune reconstitution through ART in this population need further exploration. Indeed, in a mouse model, bone loss is confirmed in the trabecular compartment in immune-reconstituted mice [22]. Given that the immune system may turn destructive or restorative depending on environmental cues, further research is much needed to define the effects of dialysis on immune reconstituted activities in patients living with HIV and kidney failure.

CONCLUSION

The prevalence of ESRD in people living with HIV has increased over the last two decades in exchange for better survival against HIV. The rise of age-associated metabolic diseases in people living with HIV requires the public health focus to address the age and treatment-associated comorbidities such as kidney disease and osteoporosis. Considering the strong proclivity for patients living with HIV to develop kidney disease and kidney failure, it is of salient public health interest to understand the effects of dialysis on bone density in immune-reconstituted patients living with HIV.

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