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Letter to the Editor

Bone impairment in HIV-infected patients and tenofovir-induced osteomalacia as a differential diagnosis

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Bone impairment is well described in people living with HIV and taking antiretrovirals due to direct and indirect effects of both the virus and the medications on bone and immune cells[1,2]. Osteopenia and osteoporosis have a prevalence of up to 67% in this population[3], and is frequent even in antiretroviral-naïve patients[2].

Such finding could suggest that unchecked viremia affects bone metabolism through its persistent systemic inflammatory properties[1]. However, an *in vitro* study showed that HIV promotes direct osteoblast apoptosis through TNF-alpha activation[4], providing evidence that bone impairment may be explained by viremia itself.

Hence, the use of antiretrovirals with a goal of undetectable viral load should lead to higher bone mineral density, but some of them may also affect bone metabolism. Indeed, a meta-analysis found that osteoporosis had an odds ratio of 2.5 in patients treated with antiretrovirals, compared to those without treatment[3], which suggests that such medications are responsible for another component of bone loss in HIV patients.

Protease inhibitors are the antiretrovirals that most frequently affect bone homeostasis: reduced bone mineral density is significantly more common in patients treated with such medications, compared to those in other treatment schemes[3]. However, tenofovir alone was also associated with increase in bone turnover markers and accelerated bone mineral density loss[5,6], even when used in the absence of HIV infection[7].

In addition to affecting bone resorption, tenofovir may also induce proximal renal tubular toxicity and hypophosphatemic osteomalacia[8], another factor that could contribute to bone alterations in HIV patients. Increased tenofovir concentrations in proximal renal tubule cells induces mitochondrial dysfunction, which leads to phosphate depletion[9]. Tenofovir-induced proximal renal tubular acidosis has an estimated prevalence of 17% in HIV-infected patients taking the drug[8], and may appear years after treatment initiation[10]. Approximately 0.5% develop hypophosphatemic osteomalacia, especially if its use is concomitant with ritonavir-boosted protease inhibitors and non-steroidal anti-inflammatories[11].

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The most common clinical finding is diffuse bone pain due to multiple stress fractures[11], and should be suspected whenever low phosphate serum levels, increased alkaline phosphatase and increased fractional excretion of phosphate are found, which rule out osteoporosis, that presents without electrolyte laboratory alterations[12]. Making the right diagnosis prevents inappropriate treatment with bisphosphonates, which depletes even more phosphorus, leaving no substrate with which to mineralize the bone, worsening pain and fractures.

Therefore, clinicians should be alert to hypophosphatemic osteomalacia in patients with low BMD receiving tenofovir, since it can be easily mistaken and incorrectly treated as osteoporosis, worsening bone pain, fractures and hypophosphatemia.

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