Bone Loss During HIV Treatment: A Possible Side Effect of CD4 Cell Recovery

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Bone loss may occur in people living with HIV during the first three months of therapy, according to new research involving humans and mice conducted at Emory University in Atlanta exploring the role of antiretroviral (ARV) therapy–induced immune activation on bone metabolism. These results, which suggest that early bone protection therapy may offset possible damage, were reported by Ighovwerha Ofotokun, MD, in an elegant presentation on Monday, February 28, at the 18th Conference on Retroviruses and Opportunistic Infections in Boston.

A number of studies have documented that accelerated bone loss—usually a consequence of aging—can occur during ARV treatment. What has been intriguing to scientists is that it isn't usually a long-term complication of HIV therapy, but rather a short-term observation. According to at least three studies, bone mineral density (BMD) can decrease by up to 4 percent following ARV treatment commencement, whereas BMD measurements are more stable in those who have been on HIV therapy for long periods of time.

Ofotokun and his colleagues hypothesize that this initial—and sometimes pronounced—drop in BMD during the first several months of treatment may be a result of the intense burst of immune activation that typically occurs once ARV treatment is started and CD4 cells attempt to regain their strength and numbers. One theory to support this hypothesis is that CD4 cell activation plays a role in the secretion of a chemical messenger called receptor activator of nuclear factor-kB ligand (RANKL), which is known to stimulate cells called osteoclasts. These cells are responsible for breaking down bone when the body needs calcium. During periods of intense CD4 cell activation—such as when the immune system is trying to recover once ARVs are started—osteoclast activity may overshadow the activity of another group of cells called osteoblasts, responsible for depositing mineral back into bones.

To explore this further, Ofotokun's group conducted two sets of experiments: one in humans to explore when BMD loss occurs following ARV therapy commencement and a second study, involving mice, exploring how immune activation affects bone loss.

The human study, involving 20 volunteers starting ARV treatment for the first time, found that blood markers of bone loss (mineral resorption) increased soon after HIV therapy was started, usually within two weeks. For example, there was a 120 percent increase in the levels of carboxy-terminal collagen crosslinks (CTx) after 12 weeks, a sign of bone collagen being broken down.

RANKL levels increased by 150 percent by week 24 of treatment, and levels of tumor necrosis factor-alpha (TNF-a), a marker of immune activation, increased by 70 percent after nearly six months of therapy.

Levels of osteocalcin, a marker of bone formation, increased by 300 percent by week 24, suggesting an intensive effort by osteoblasts to rebuild bone.

The rodent study involved mice deficient in T-cell receptor-beta (TCR-b), the protein on CD4 cells most closely associated with increased RANKL production during immune activation. Markers of bone resorption, along with dual energy x-ray absorptiometry (DEXA) and CT scans, were checked before and after infusing the mice with normal T cells.

As in the human study, markers of bone resorption were documented in the mice after 12 weeks, including a 150 percent increase in CTx, a 60 percent increase in RANKL and a whopping 344 percent increase in TNF-a. Unlike humans, however, there was a decrease in osteocalcin levels, indicating limited osteoblast activity to replace bone mineral broken down by osteoclasts.

The scans, also conducted at 12 weeks, found that BMD of the mice thigh bones decreased by about 10 percent, with loss also documented in shin bones and spines. There was also a 40 percent drop in the volume of both the spongy (trabecular) and hard (cortical) elements of bone.

Ofotokun noted that his group’s data are still preliminary and the results of these studies are still being analyzed. For example, he noted that some patients in the study took tenofovir (found in Viread, Truvada and Atripla), a commonly used nucleotide analogue that has been associated with accelerated bone loss. Whether study volunteers taking tenofovir were more or less likely to have increased levels of bone metabolism markers has not yet been determined.

Still, he concluded his lecture by stating that immune activation immediately following the commencement of ARV treatment—which may be dependent on the degree of immune activation that occurs—is associated with BMD loss. If these observations prove correct, it may be useful to employ therapies to offset bone loss at the time ARV treatment is started.
