BONE

High 27-hydroxycholesterol decreases BMD

An endogenous selective estrogen receptor modulator, 27-hydroxycholesterol, has a negative influence on bone homeostasis, according to a research team from the USA.

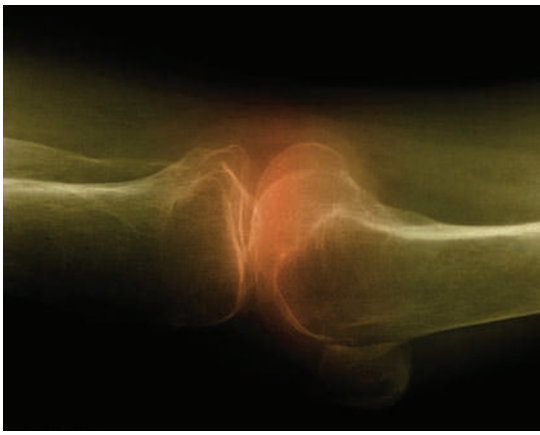
"Osteoporosis is an important public health concern, and it is well known that estrogens have a protective role in bone," explain lead researchers Carolyn Dusell and Erik Nelson (Duke University Medical Centre, Durham, USA). The researchers have previously found that 27-hydroxycholesterol (a cholesterol metabolite) interacts with the estrogen receptor and modulates its activity. This finding, together with reports of an association between metabolic disease and osteoporosis, and improved BMD in patients treated with statins, led the researchers to examine the impact of this oxysterol on skeletal integrity.

> "...patients at risk of osteoporosis should limit their cholesterol intake..."

The investigators used two genetically altered mouse models to assess the effect of either absence of 27-hydroxycholesterol or pathologically raised levels of 27-hydroxycholesterol. One model lacked the enzyme that synthesizes 27-hydroxycholesterol, whereas the other model lacked the enzyme that metabolizes it. To eliminate any confounding effects the investigators also directly increased levels of the oxysterol by daily injection of mice lacking the metabolizing enzyme with 27-hydroxycholesterol for 28 days. Urine, blood and bone tissue samples were then analyzed.

Increasing the 27-hydroxycholesterol concentration led to decreased BMD, which was associated with both decreased bone formation and increased bone resorption. To evaluate whether these effects were owing to the interaction of 27-hydroxycholesterol with the estrogen receptor, the researchers tested the effect of estradiol administration on BMD in the mice with raised levels of 27-hydroxycholesterol. Ovariectomized mice received daily injections of either placebo or 10 μg/kg of 17β-estradiol; administration of the hormone restored normal BMD. Some pathologies associated with raised levels of 27-hydroxycholesterol, such as loss of cortical bone, were exacerbated in the ovariectomized mice. Primary cultures of preosteoblasts showed that 27-hydroxycholesterol acts as a partial estrogen receptor agonist.

These findings suggest that 27-hydroxycholesterol is a key component in the interaction between cholesterol levels and BMD. The researchers state that 27-hydroxycholesterol "acts to reduce estrogen signaling at the level of the estrogen receptor and possibly by other pathways to negatively impact bone."



The researchers are currently investigating the mechanisms of action of 27-hydroxycholesterol in bone and the association between raised cholesterol levels or metabolic disease and decreased BMD.

"This paper suggests that patients at risk of osteoporosis should limit their cholesterol intake, and justifies the development of therapeutics targeting the synthesis or metabolism of 27-hydroxycholesterol," they conclude.

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Original article Dusell, C. D. *et al.* The endogenous selective estrogen receptor modulator 27-hydroxycholesterol is a negative regulator of bone homeostasis. *Endocrinology* **151**, 3675–3685 (2010)