Cholesterol contributes to bone loss during aging

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(Medical Xpress) -- High cholesterol has been found to contribute to a loss of bone density in two ways, according to researchers at Duke University Medical Center. It blocks formation of new bone cells and it encourages the activity of mechanisms responsible for breaking down bone.

The findings, from studies on mice, open new possibilities for the treatment and prevention of osteoporosis and highlight a possible new way that cholesterol-lowering statin drugs may improve bone health.

"For years, people thought that the positive effects of statin drugs on bone mineral density occurred independently of their ability to lower circulating cholesterol," said Donald McDonnell, Ph.D., chair of the Duke Department of Pharmacology and Cancer Biology. "The question was: had scientists explored whether lowering cholesterol actually impacted bone biology? They hadn't. When you hear hooves, think horses, not zebras – look for a more obvious explanation."

Instead of focusing on cholesterol itself, the Duke researchers focused on a breakdown product of cholesterol called 27-hydroxycholesterol, and demonstrated that this molecule actually inhibited the positive actions of estrogens on bone.

"In the current study in mice, we showed that a high-cholesterol diet alone significantly decreased bone quality," said Erik Nelson, Ph.D., a postdoctoral research associate in the McDonnell laboratory. However,

they noted that only when cholesterol was converted to 27-hydroxycholesterol did it negatively impact bone.

"We found that by binding to the estrogen receptors, 27-hydroxycholesterol interferes with the positive actions of estrogens in bone," Nelson said. "We also found that a second class of proteins, liver X receptors, were targets of 27-hydroxycholesterol in bone. The combined actions of this byproduct of cholesterol on the estrogen receptors and liver X receptors resulted in a doubly harmful impact on bone."

They found that supplemental estrogen could improve bone density in mice with elevated 27-hydroxycholesterol, noting that estrogens induced the expression of a protein called SHP in developing bone cells that inhibited the negative activity of the liver X receptor.

Without estrogen, which occurs in postmenopausal women, the 27-hydroxycholesterol continued signaling through liver X receptor, which decreased the amount of bone.

"Although estrogens have been used for years for the treatment and prevention of post-menopausal osteoporosis, the mechanisms by which it accomplished its positive actions were unclear," McDonnell said. "These data not only provide an explanation for this positive activity of estrogen but also highlight new approaches that can be used to treat this disease."

Nelson said there are drugs that can artificially increase the amount of SHP, which stops this bone-loss process, so it may be possible to develop therapeutics that have a similar effect in humans.

"In the meantime, the data we have generated thus far suggest an unanticipated positive activity of statins and add to the list of health benefits associated with lowering cholesterol," McDonnell said.

Provided by Duke University