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BONE

OXIDATIVE STRESS AND OSTEOPOROSIS

NADPH oxidase 4 (NOX4) promotes osteoclastogenesis in mice, new data reveal. Inhibition of this enzyme might, therefore, hold potential to attenuate bone loss in osteoporosis.

Reactive oxygen species have been linked to bone loss, but the specific mechanisms and key players involved are unclear. NOX4 is constitutively active and produces the reactive oxygen species hydrogen peroxide. Senior researcher Katrin Schröder of Goethe University Frankfurt, Germany and co-workers investigated the role of NOX4 in bone loss in mice and humans.

The researchers found that Nox4-deficient mice had increased BMD. "Obvious questions arose from this finding," explains Schröder, "including whether the increased BMD was due to increased bone formation or reduced resorption, the underlying mechanisms involved, and whether the findings in mice were also valid for human bone."

Further experiments in the Nox4-deficient mice revealed that the increased BMD was associated with a reduced number of osteoclasts and, consequently, reduced bone resorption. Moreover, the process of osteoclastogenesis was dysfunctional in Nox4-deficient mouse cells *in vitro*, suggesting that Nox4 promotes osteoclastogenesis.

A causal role for Nox4 in osteoporosis was then tested in a mouse model of ovariectomy-induced osteoporosis. In these mice, acute genetic knockdown of *Nox4* or administration of a Nox4 inhibitor attenuated bone loss.

NOX4 also seems to be linked to bone loss in humans. Expression of NOX4 was increased in bone material from patients with untreated osteoporosis, compared with bone material from healthy individuals. Furthermore, a single nucleotide polymorphism of *NOX4* was associated with elevated levels of circulating markers of bone turnover, including osteocalcin and alkaline phosphatase, and reduced BMD in middle-aged women.

"Osteoporosis in humans is a chronic and highly complex disease," concludes Schröder. "Nevertheless, the findings of the current study suggest that NOX4 inhibitors should be investigated further for this indication."

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Original article Goettsch, C. *et al.* NADPH oxidase 4 limits bone mass by promoting osteoclastogenesis. *J. Clin. Invest.* doi:10.1172/JCI67603