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A crucial role for thiol antioxidants in estrogen-deficiency bone loss.

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Abstract

The mechanisms through which estrogen prevents bone loss are uncertain. Elsewhere, estrogen exerts beneficial actions by suppression of reactive oxygen species (ROS). ROS stimulate osteoclasts, the cells that resorb bone. Thus, estrogen might prevent bone loss by enhancing oxidant defenses in bone. We found that glutathione and thioredoxin, the major thiol antioxidants, and glutathione and thioredoxin reductases, the enzymes responsible for maintaining them in a reduced state, fell substantially in rodent bone marrow after ovariectomy and were rapidly normalized by exogenous 17-beta estradiol. Moreover, administration of N-acetyl cysteine (NAC) or ascorbate, antioxidants that increase tissue glutathione levels, abolished ovariectomy-induced bone loss, while l-buthionine-(S,R)-sulphoximine (BSO), a specific inhibitor of glutathione synthesis, caused substantial bone loss. The 17-beta estradiol increased glutathione and glutathione and thioredoxin reductases in osteoclast-like cells in vitro. Furthermore, in vitro NAC prevented osteoclast formation and NF-kappaB activation. BSO and hydrogen peroxide did the opposite. Expression of TNF-alpha, a target for NF-kappaB and a cytokine strongly implicated in estrogen-deficiency bone loss, was suppressed in osteoclasts by 17-beta estradiol and NAC. These observations strongly suggest that estrogen deficiency causes bone loss by lowering thiol antioxidants in osteoclasts. This directly sensitizes osteoclasts to osteoclastogenic signals and entrains ROS-enhanced expression of cytokines that promote osteoclastic bone resorption.

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