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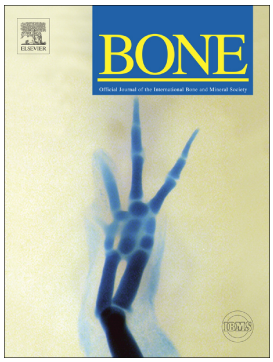

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ACCEPTED MANUSCRIPT

IL-6 *trans*-signalling mediates trabecular, but not cortical, bone loss after ovariectomy

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Abstract

Bone loss associated with estrogen deficiency occurs due to a high level of bone remodelling, with a greater increase in the level of osteoclast-mediated bone resorption than osteoblast-mediated bone formation. Early studies showed that Interleukin-6 (IL-6) inhibition could prevent the increase in osteoclast numbers associated with ovariectomy. However, IL-6 signals through two possible pathways: classic IL-6 signalling (*cis*) utilizes a membrane-bound IL-6 receptor (IL-6R), while IL-6 *trans*-signalling occurs through a soluble IL-6R (sIL-6R). It is not known which of these pathways mediates the bone loss after ovariectomy. We therefore sought to determine whether specific pharmacological inhibition of IL-6 *trans*-signalling could prevent ovariectomy-induced bone loss in mice. We report that IL-6 *trans*-signalling inhibition prevented the increase in osteoclasts, and trabecular bone loss, associated with ovariectomy. IL-6 *trans*-signalling inhibition also reduced bone formation rate, but did not prevent the increase in osteoblast numbers. In contrast, cortical bone loss was not prevented by any IL-6 signalling inhibitor. This suggests that local production of sIL-6R mediates

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