

## **The Pituitary-Bone Axis**

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Osteoporosis is a public health hazard that affects 44 million women. The incidence of postmenopausal osteoporosis has been thought to arise from low estrogen levels. We have revisited the pathophysiology of postmenopausal bone loss that results from estrogen deficiency and osteoporosis in hyperthyroidism thought to result from elevated thyroid hormone levels. In these states, pituitary hormones, namely FSH (follicle stimulating hormone) and TSH (thyroid stimulating hormone), are reciprocally regulated by feedback. Thus, estrogenic feedback during the menopause causes an elevation of FSH and feedback by elevated thyroid hormones lowers TSH, often to undetectable levels, in hyperthyroidism. We have evaluated the direct actions of FSH and TSH on bone and bone cells and suggest that elevated FSH and lowered TSH levels *contribute* to the bone loss in hypogonadal and thyrotoxic states. We find that haploinsufficiency of FSH and the TSH receptor in heterozygotic mice, which have conserved ovarian and thyroid function, display high and low bone mass, respectively. This suggests that the actions of FSH and TSH on the skeleton are independent of the action of the hormones they release from the ovary and thyroid gland, respectively. We have identified both FSH and TSH receptors on osteoclasts, while we can detect only TSH receptors on mature osteoblasts. Activation of the TSH receptor causes a dramatic reduction in osteoclast formation, bone resorption and osteoclast survival through the inactivation of MAP kinase and NF- $\kappa$ B signalling. The reverse occurs with FSH in both mouse and human osteoclast cultures. Epidemiologic studies reveal a close correlation between fracture risk and serum TSH levels in hyperthyroid patients. Furthermore, patients with TSH receptor mutations have bone loss despite being rendered euthyroid with thyroxine therapy. Recombinant human TSH inhibits bone turnover in postmenopausal women. Clinical data implicating elevated FSH in the genesis of postmenopausal osteoporosis has evolved. Strong correlations nonetheless exist between bone mass and FSH levels across the menopausal transition. Furthermore, amenorrheic women with high, but not low/normal FSH levels experience bone loss. Together, these studies implicate anterior pituitary hormones in the direct control of bone cell function in skeletal health and disease.