Cold stress and high fat, high protein diet decreases trabecular and cortical bone mass in male C57BL/6J mice

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Chronic cold stress is associated with accelerated age-related bone loss in circumpolar human populations, but the mechanisms involved remain unclear. Cold exposure upregulates the sympathetic nervous system, which can cause bone loss via osteoblast beta-adrenergic receptors. However, sympathetic activation also increases nonshivering thermogenesis (NST) via uncoupling protein-1 (UCP1) in brown adipose tissue, which should increase body temperature, decrease sympathetic activation, and reduce bone loss. The goal of this study is to understand the role of sympathetic tone and NST in mediating the skeletal effects of cold exposure. We used a mouse model to test three hypotheses: that sympathetic activation is a cause of cold-induced bone loss; that blocking sympathetic tone during cold exposure reduces bone loss; and that the high fat, high protein diet traditionally consumed by circumpolar humans can decrease cold-induced bone loss by providing additional calories for NST. To test these hypotheses, we compared skeletal phenotype in three groups of male C57BL/6J mice: 1) cold exposed, 2) cold exposed with sympathetic inhibition, and 3) cold exposed with high fat, high protein (HFHP) or normal (N) diet (all N=8/group). All mice were pair housed at 16°C (moderate cold stress) or 26°C (thermoneutrality) from 3–12 wks of age with food ad libitum. Groups assigned to sympathetic inhibition were treated with the beta-adrenergic inhibitor propranolol in drinking water ad libitum (0.5 mg/mL). Groups assigned to HFHP diet were fed a calorie composition of 40% protein, 40% fat, and 20% carbohydrate, vs. the N diet of 20% protein, 10% fat, and 70% carbohydrate. We used general linear models to test for effects of temperature, propranolol, diet, and their interactions. Results indicate that 1) cold exposure decreased trabecular bone microarchitecture and cortical bone mass at 16°C vs. 26°C, despite increased core body temperature and higher UCP1 expression. 2) In mice at 16°C, propranolol prevented loss of both trabecular and cortical bone, despite significantly decreased UCP1 expression and unchanged body temperature. At 26°C, propranolol had no effect on bone mass, body temperature, or UCP1. 3) HFHP mice at 26°C but not 16°C gained more body mass and body fat vs. N. HFHP mice had markedly lower trabecular bone volume fraction at both 16°C and 26°C, as well as lower cortical bone area fraction and cortical thickness at 16°C, compared to N mice. These data show that prolonged cold stress decreases trabecular and cortical bone mass in mice even when nonshivering thermogenesis is increased. Blocking sympathetic tone prevents bone loss despite reduced nonshivering thermogenesis. High fat, high protein diet increases nonshivering thermogenesis and body fat, but is deleterious to trabecular bone both during cold exposure and at thermoneutrality. These findings support our hypothesis that sympathetic activation contributes to cold-induced bone loss in humans, but do not support our hypothesis that high fat, high protein diet might protect against cold-induced bone loss, and suggest such diets may be detrimental to human bone health.

Funding: NSF BCS-1638553