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EFFECTS OF INHIBITING BONE RESORPTION ON MUSCLE ATROPHY DURING UNLOADING

Abstract

Muscle and bone disuse during extended periods of unloading leads to atrophy of both tissues, especially in conditions such as long-duration spaceflight. While bone and muscle atrophy are often researched together in the context of their force-transmitting interaction during exercise or unloading, the non-mechanical (biological) crosstalk of these tissues has not been as well characterized. During disuse, osteoclasts break down existing bone tissue, releasing osteokines such as transforming growth factor beta (TGF-) and Receptor activator of NF-B (RANK) ligand (RANKL), both of which initiate myopathy through their respective pathways. Determining whether these osteokines drive atrophy of muscle separate from the effect of reduced mechanical stimulus could further define the biological crosstalk between bone and muscle. To investigate bone-muscle crosstalk during mechanical unloading, we used hindlimb unloading (HLU) of young (3 month old, n = 20) or middle-aged (12 month-old, n = 20) mice that were treated with either alendronate (1.0 mg/kg twice per week s.c., n = 10 per age group) to inhibit bone resorption or were treated with vehicle (phosphate buffered saline (PBS), n = 10 per age group). Cortical and trabecular bone microstructure were quantified with micro-computed tomography, muscle mass, composition and force generation, and tendon mechanical behavior were performed and compared to control mice undergoing normal cage activity (to treatment n = 20, PBS injection n = 20, bisphosphonate injection n = 20, with n = 10 per age group). Osteokine levels were also assessed in bone and muscle tissue, as well as in serum via ELISA. We hypothesized that inhibiting bone resorption would prevent the release of osteokines and reduce muscle tissue atrophy during unloading. Consistent with this hypothesis, during our preliminary data analysis we confirmed that alendronate injections maintained bone volume in the femoral diaphysis and metaphysis during HLU. Additionally, we found that bisphosphonate treatments in middle-aged mice show increased max muscle force for the Tibialis anterior (mN/mg) and max force for body weight (mN/g) compared to untreated HLU groups. Findings from this study expand our understanding of bone-muscle crosstalk during unloading, and could lead to the development of treatments to prevent bone and muscle atrophy during spaceflight and long-duration missions in fractional gravity environments.