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Utilizing Dynamic Histomorphometry to Evaluate Bone Formation in Mouse Femurs Following Myostatin Inhibition

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Osteogenesis Imperfecta (OI) is a hereditary connective tissue disorder due primarily to type I collagen mutations. Characterized by frequent fractures and bone fragility, OI, is colloquially known as “brittle bone disease.” Currently, OI is incurable, and the most common treatment is bisphosphonates, an antiresorptive agent, which inhibits osteoclasts, cells vital to bone remodeling. Bone remodeling is necessary for maintaining healthy bone by removing and replacing damaged bone. Without osteoclast pruning, normal bone remodeling and growth does not occur, leading to decreased bone quality and compromised bone structure. Myostatin inhibition provides a potential solution to this problem. Bone is in a biomechanical/biochemical equilibrium with muscle, responding to changes in muscle size and force. Myostatin negatively regulates muscle mass. A decrease in circulating myostatin results in increased muscle mass and strength, increasing the force exerted on the bone, culminating in increased bone mass. This study hypothesizes that Myostatin inhibition will stimulate osteoblast activity and bone growth without compromising osteoclast function, resulting in increased bone quality and bone quantity. Previous studies show that myostatin inhibition significantly improves bone microarchitecture and strength. To investigate myostatin inhibition on osteoblast function in wildtype (Wt) mice, we evaluated femoral cortical bone formation rates (BFR) and mineral apposition rates (MAR) to elucidate the mechanism for this increased bone mass. Beginning at five weeks of age, Wt mice were weighed and injected twice weekly with humanized monoclonal control or anti-myostatin antibody (10 mg/kg of body weight) for 11 weeks. To evaluate the change in MAR and BFR, a calcein label and an alizarin red label were administered 10 and 3 days before euthanization. Through histological evaluation of the amount of fluorescent labeling and distance between the fluorescent labels (ImageJ software), we can determine whether the increased bone mass found with myostatin inhibition is due to increased bone formation.