Impact of excess TGFβ on bone and muscle in condition of diet-induced obesity in mice with Camurati-Engelmann Disease

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**Background and Hypothesis:** Camurati-Engelmann Disease (CED) is characterized by extreme bone turnover and excess TGF-β release. We previously showed that bone-derived TGF-β causes glucose intolerance, increases skeletal muscle weakness, and exacerbates diet-induced obesity in CED mice. However, it is unknown whether glucose intolerance and obesity alter bone and muscle phenotypes. Thus, we hypothesized that impaired glucose metabolism and diet-induced obesity exacerbate bone and muscle loss in a mouse model of CED.

**Experimental Design:** 45-week WT and CED mice were fed either high-fat diet (HFD) or low-fat diet (LFD) for 15 weeks. Ex vivo bone micro-CT and histomorphometry were used to evaluate bone and muscle. Statistical analysis was performed using GraphPad Prism with p<0.05 considered significant.

**Results:** CED mice showed severe cortical and trabecular bone loss in response to diet-induced obesity. Trabecular bone volume was reduced by 37% in L5 vertebrae (p<0.001), 16% in tibiae (p<0.05), and 7% in femora in CED-HFD compared to WT-HFD. Bone mineral density was reduced (p<0.0001) and cortical porosity was increased (p<0.0001) in CED-HFD vs WT-HFD in femora and tibiae. Bone histomorphometry showed no significant differences in osteoclast number between groups. pSMAD2/3 staining was increased by 25% (p<0.05) and muscle fiber diameter was reduced by 32% (p<0.05) in the tibialis anterior muscle of CED mice compared to WT, with greater changes in HFD-fed mice.

**Conclusion and Potential Impact:** High-fat diet and impaired glucose metabolism exacerbates bone loss and increases TGF-β signaling in CED mice. In future studies, inhibiting TGF-β signaling and reducing adiposity may prevent glucose intolerance and musculoskeletal deterioration in conditions of high bone turnover.