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.