Bone Blood Perfusion Increases with Diet-Induced Obesity, Associated with Trabecular Deterioration in Mice

Nicholas J. Hanne[1], Andrew J. Steward[1], Elizabeth D. Easter[2], and Jacqueline H. Cole[1]
[1]Joint Department of Biomedical Engineering, North Carolina State University and University of North Carolina, Raleigh, NC, [2]Materials Science and Engineering Department, North Carolina State University, Raleigh, NC

Introduction: In addition to cardiovascular problems (e.g., peripheral artery disease, ischemic stroke), individuals with obesity and metabolic disease experience higher bone fracture rates, despite having greater bone mass than healthy individuals. We hypothesized that vascular changes with obesity are systemic and, because vascular function is critical for bone development and repair, changes to vasculature within bone contribute to decreases in bone health with obesity. Further, exercise stimulates vascular growth and performance and may be an effective intervention to ameliorate chronic changes in bone vasculature [1]. We aim to correlate changes in trabecular architecture with changes in bone vasculature due to obesity and exercise.

Materials and Methods: We induced obesity in eight five-week-old, male C57Bl/6J mice using a high-fat diet (HFD, D12492, Research Diets, New Brunswick, NJ) for nineteen weeks, while another eight mice were fed a control-fat diet (CFD, D12450, Research Diets, New Brunswick, NJ). After ten weeks, daily treadmill exercise (9 m/min, 37 min/day) (Columbus Instruments, Columbus, OH) was initiated on half of the lean (CFD) and half of the obese (HFD) mice to examine the effects of exercise therapy on bone blood perfusion and trabecular bone density and architecture. Before sacrifice, *in vivo* blood perfusion was measured in the tibial proximal metaphysis using minimally invasive laser Doppler flowmetry (LDF). LDF has been previously validated for measuring functional perfusion in murine tibiae beyond what can be measured by serum protein concentrations or histology of vasculature [2]. After sacrifice, femora were dissected and scanned with micro-computed tomography (μCT 40, SCANCO Medical, Brüttisellen, Switzerland). Scans were reconstructed at a 10-μm voxel size, and metaphyseal density and architecture were quantified [3]. For the LDF and micro-CT metrics, the effects of diet and exercise were examined using two-way ANOVA with Tukey post-hoc (R). The relationships between vascular and bone metrics were assessed with correlations. Significance was set at α=0.05.

Results and Discussion: LDF measurements detected increased tibial blood flow with both treadmill exercise (exercise vs. sedentary) and diet (obese vs. control) (Fig. 1). Micro-CT analysis determined that treadmill exercise had no effect on trabecular architecture in the femoral metaphysis. With HFD, however, bone volume fraction decreased 31.5% (p=0.007) and trabecular number decreased 19.6% (p=0.0006).

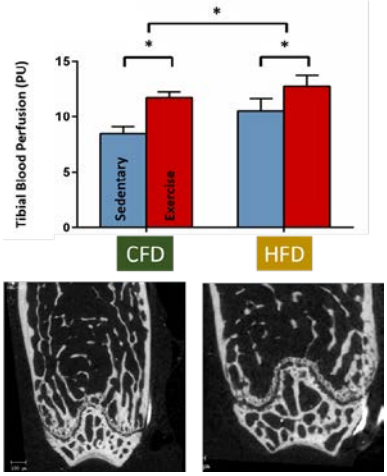

Fig. 1. Laser Doppler flowmetry measures of tibial blood perfusion. Relative to sedentary, exercise mice had increased perfusion with both control-fat (+38%) and high-fat (+21%) diets. In sedentary mice, diet-induced obesity (HFD) increased perfusion 24%. n = 4 per group, * $p < 0.05$.

Conclusions: These results indicate that diet-induced obesity causes trabecular deterioration within the distal femoral metaphysis in mice. Obesity was also associated with greater blood perfusion. Increased perfusion in the tibial metaphysis may result from decreased cortical bone or an environment that favors blood flow to stimulate bone growth. Moderate treadmill exercise may increase bone blood flow in obese and lean mice but is not sufficient to reverse the bone loss associated with obesity or reverse weight gain. Future work will utilize nano-computed tomography to visualize and quantify the capillary structures within bone and correlate vascular structure with function blood perfusion and also bone morphology.

References:

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3. Bouxsein M, *JBMR* (2010) 25.7:1468