Ketogenic Diet Alters the Musculoskeletal and Cardiac Response to Voluntary Wheel Running in Growing Male Mice

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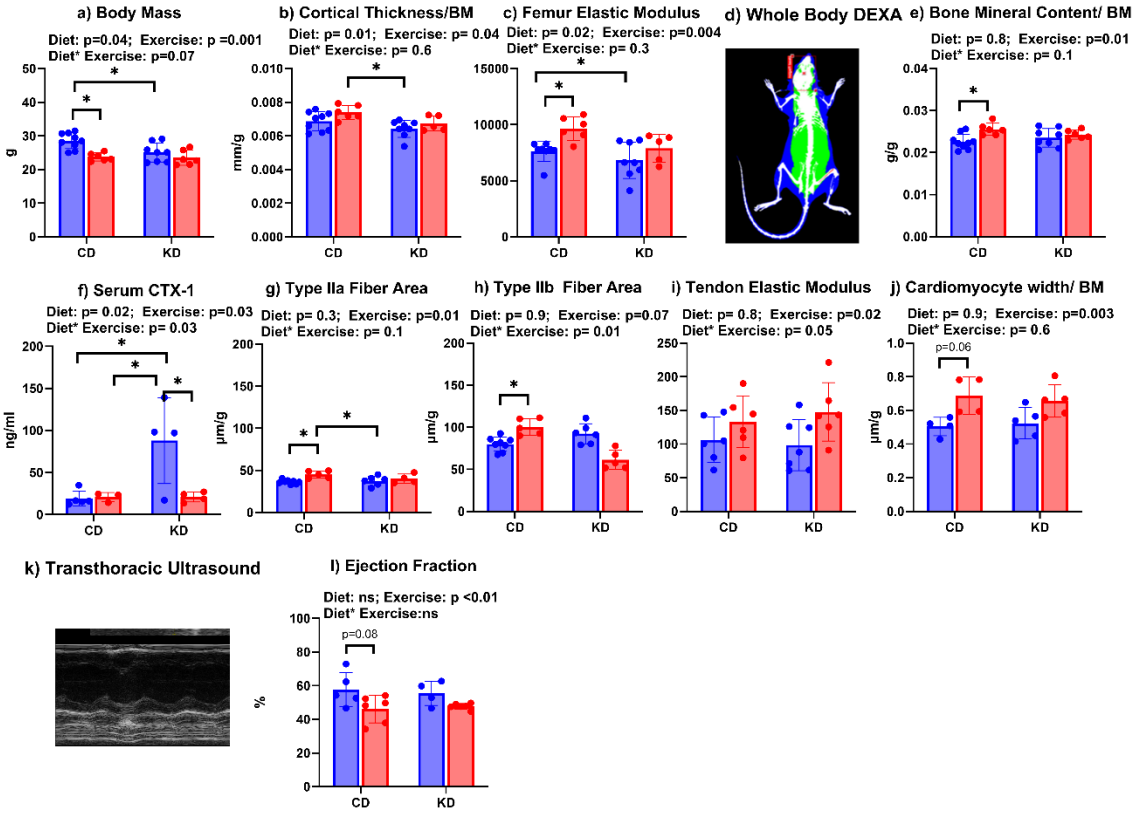
INTRODUCTION: Ketogenic Diet (KD), a diet high in fat and low in carbohydrate, is associated with bone loss in children prescribed KD for drug refractory epilepsy, and we have previously shown it causes bone loss in both growing and adult mice. Furthermore, prior studies in athletes found that KD decreased markers of bone formation and increased markers of bone resorption. Previous studies disagree if KD has a deleterious or beneficial effect on muscle mass and heart function. In this study, we assessed the effect of KD and exercise on musculoskeletal and cardiac tissue. We hypothesized that compared to animals eating a control diet (CD), KD mice would exhibit reduced bone, muscle, tendon, and heart size and functional properties. Also, we hypothesize that KD would reduce the anabolic response to exercise in these tissues.

METHODS: This study used a total of 32 male 4-week-old C57BL/6J mice. Animals were placed on an ad-libitum KD or control diet (CD). Mice were then randomly assigned to normal cage activity or placed in a modified cage with free access to a running wheel. Mice were subsequently euthanized at 8 weeks after start of exercise intervention. Bone and body composition changes were quantified using Dual X-Ray Absorptiometry (DEXA), microCT, and serum markers of bone remodeling. 3 point bending of the femur midshaft and tensile testing of tendon quantified bone and tendon strength. Gastrocnemius and soleus muscle fiber size and type were quantified using immunohistochemistry. Cardiac function was measured using transthoracic echocardiography and in-vivo measurement of cardiomyocyte diameter at 6 weeks after exercise start. Two-way ANOVA with exercise and diet as factors and Tukey HSD for post-hoc comparisons was used to compare groups.



RESULTS: After 8 weeks, CDE and both KD groups weighed less than CDS animals and KDE did not weigh less than KDS (a). After standardizing for difference in body mass, KD mice showed significantly reduced femur cortical thickness and elastic modulus (Diet: $p<0.05$) (b,c). Also, exercise significantly increased bone mineral content and femur elastic modulus in CD but not KD mice (c-e). Serum C-terminal telopeptide of type 1 collagen (CTX1), the marker of bone resorption was elevated in KDS mice compared to KDE, CDS and CDE (f). Exercise significantly increased body size standardized muscle fiber area in CD mice but not KD mice, and this difference was evident in both IIa (oxidative) and IIb (glycolytic) fibers (g,h). Exercise increased tendon elastic modulus, but there was no effect of diet (i). Exercise significantly increased cardiomyocte diameter (j) and decreased ejection fraction (k-l). CDE mice showed a trend toward greater cardiomyocyte diameter ($p=0.06$) and ejection fraction than CDS ($p=0.07$), but KDE was not significantly different from KDS (j,l).

CLINICAL IMPLICATIONS: KD was associated with declines in bone properties and bone remodeling not fully accounted for by differences in body size. Furthermore, the effect of exercise on bone, skeletal muscle and cardiac muscle was larger in CD compared to KD mice. However, exercise reduces serum markers of bone resorption in KD mice, indicating that exercise may still reduce KD induced bone loss. Wheel running alters tendon mechanical properties. These results suggest that KD may significantly increase osteoporosis risk. Also, KD may blunt the anabolic effects of exercise on bone, skeletal muscle, and cardiac muscle. This finding may be of concern to individuals seeking to enhance athletic performance or avoid injuries during athletic training.

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