Influence of Resistance Running on Quadriceps Strength and Femur Bone Quality in Skeletally Mature Male Wistar and Lewis Rats

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INTRODUCTION: Exercise is one of the most commonly prescribed treatments to prevent and treat musculoskeletal diseases. There are two main types of exercise that are prescribed, aerobic and resistance exercise. Aerobic exercise, such as walking and running, focuses on improving cardiovascular function; while resistance exercise, such as squats, focuses on enhancing muscle strength[1]. These can be modulated by changing the intensity, duration and timing of exercise intervention. Clinically, there is a lack of consensus on the best exercise regime to help treat different diseases. To better understand how these parameters affect disease, animal models can be used to systemically study these in a controlled environment. One current limitation of animal models is that most exercise regimes used to study musculoskeletal diseases focus on aerobic exercise modalities, such as treadmill running or voluntary wheel running. To combat this, resistance exercise models have been developed to better mimic the muscular targeting seen in clinical resistance exercise[2]. This study utilizes a resistance running paradigm to examine lower limb muscle adaptations, quadriceps isometric torque, and bone adaptations in naïve rats. *We hypothesized that the addition of resistance will result in an increase in quadriceps isometric torque and femur bone mineral density in both the Lewis and Wistar rats.*

METHODS: Skeletally mature male Lewis (376.5±12.4 g) and Wistar (378.2±14.7 g) rats were chosen to ensure full musculoskeletal development and reduce variability associated with hormonal cycling when evaluating mechanical loading responses. Animals were introduced to exercise using Scurry Rat Activity Wheels (Lafayette Instrument) with or without the addition of a custom-made brake system for unlimited wheel access for 4 hours/day and 5 days/week for a 6-week running program under IACUC approved protocols (n=2-3/group). For the first week, all animals ran with no brake applied to the wheel. Starting at week 2, resistance equivalent to 50% of the average body weight (BW) for each cohort of rat strain was applied via the brake system for half of the animals. Resistance was increased to 80% BW in week 3, 120% BW in week 4, 150% BW in week 5, and 172% BW in week 6. The distance ran, number of bouts, and bout velocity was recorded using the Scurry Activity System (Lafayette Instrument). Following the completion of the running program, isometric torque muscle testing was done to determine maximum quadricep strength[3]. The weights of the left quadriceps, tibialis anterior (TA), and gastrocnemius were recorded, and the right femurs were harvested and scanned for µCT analysis (Scanco vivaCT; 48 mm voxels, 55 kVp, 145 mA, and 750 ms). The bone volume (BV), bone mineral density (BMD), and polar moment of inertia (pMOI) were calculated inside a standard 1.5 mm and 2.5 mm long cylindrical volume of interest (VOI) in the mid-diaphysis. *Statistical Analysis:* One-way ANOVA was used to compare groups for running parameters, muscle weights, and bone parameters. Mixed-effect analysis was used for quadriceps isometric torque.

RESULTS SECTION: When examining running parameters, Lewis rats ran approximately 1.8 times more during the daily 4 hour running period than Wistar rats in both the no resistance running and resistance running group (Fig 1A). The addition of resistance, beginning at 50% BW, resulted in a trend towards increased running bout velocity (29.98±2.404 m/s) compared to no resistance (28.19±1.87 m/s) (Fig 1B). No difference in muscle wet weight was seen in the quadriceps, TA or gastrocnemius in Wistar or Lewis rats in any treatment group (Fig 1C, E). A significant increase was seen for maximum quadriceps isometric torque between the sedentary and resistance running groups for the Wistar rats, while no difference was seen between groups for Lewis rats (Fig 1B, D). A statistical increase was seen for BV in Wistar rats between sedentary and resistance running, as well as free running and resistance running, while no difference was seen for the Lewis rats.

DISCUSSION: The addition of resistance to the voluntary running wheel paradigm improved quadriceps strength and induced bone adaptation in the femur in Wistar rats, indicating the model's effectiveness for inducing structural responses similar to those seen in human resistance exercise. The strain-specific outcomes suggest potential biological and behavioral differences between Lewis and Wistar rats, which has been seen in previous literature[4]. Despite the Lewis rats running greater total distances, they did not exhibit significant improvements in quadriceps strength or bone metrics, suggesting that training volume alone may not be sufficient to drive adaptations. One limitation of this study is that deviations might be present between muscle dissections for each animal leading to potential variation in the recorded wet weight. Additionally, the small sample size reduces the statistical power to detect subtle differences in muscle or bone parameters between the strains and running conditions.

SIGNIFICANCE/CLINICAL RELEVANCE: This work demonstrates that a voluntary resistance running model can elicit musculoskeletal adaptation, in particular quadriceps strength, in rats, establishing a translationally relevant platform for studying the mechanisms of resistance exercise. This model can be used to explore how resistance running modifies muscle strength, bone adaptations and joint health in the context of aging and musculoskeletal diseases, such as osteoarthritis.

REFERENCES: [1] Nguyen+2016 *Ann Phys Rehabil Med* [2] Legerlotz+2008 *Exp Physiol* [3] Li+2015 *J Biomech* [4] Clemens+2014 *Genes Brain Behav*

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IMAGES AND TABLES:

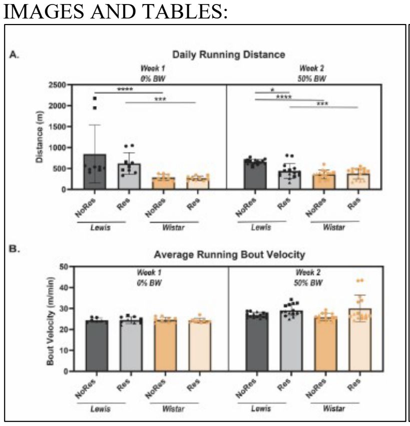

Figure 1. A. Daily distance ran in one 4-hour period at week 1 and week 2. B. Average velocity of one bout of running at week 1 and week 2. Data shown as Mean ± STD. One-way ANOVA (P<0.05)

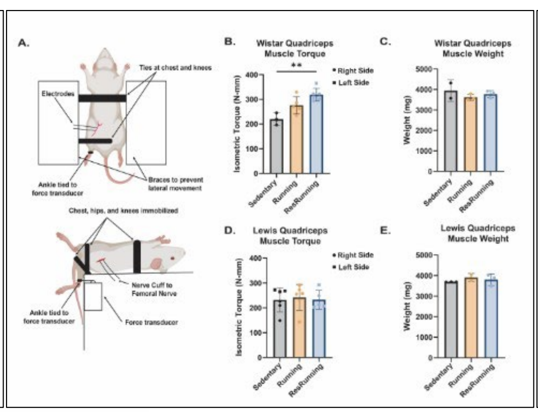

Figure 2. A. Methodology for isometric torque testing for quadriceps. B. Quadriceps isometric torque for the Wistar rats. C. Quadriceps muscle wet weight for the Wistar rats. D. Quadriceps isometric torque for the Lewis rats. E. Quadriceps muscle wet weight for the Lewis rats. Data shown as Mean ± STD. Mixed effect analysis (P<0.05)

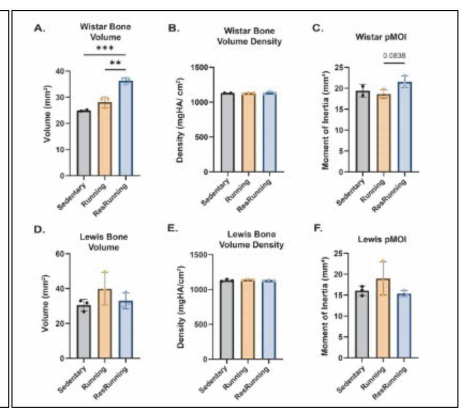

Figure 3. A. Femur bone volume for Wistar rats B. Femur bone density for the Wistar rats. C. Femur polar moment of inertia for the Wistar rats. D. Femur bone volume for Lewis rats E. Femur bone density for the Lewis rats. F. Femur polar moment of inertia for the Lewis rats. Data shown as Mean ± STD. Mixed effect analysis (P<0.05)