

EXERCISE EFFECTS VIA TREADMILL RUNNING AND TOWER CLIMBING ON FEMORAL BONES OF C57BL/6J AND DBA/2J ADULT FEMALE MICE

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INTRODUCTION

It is widely accepted that bone is able to adapt to changes in its loading environment by altering its mechanical properties. The details of this adaptation are still being explored, including the attempted elucidation of the genes involved. However, the response of bone to mechanical demand is very complex in regard to the genetic interactions within bone as well as potential indirect influences on bone via genes that affect such things as behavior, muscle force and body weight. The main focus of our study was to further explore gene-environment interactions relative to bone adaptation. Increasing our understanding of these interactions may someday enable more individualized interventions dependent on a person's genotype when preventing and treating bone disease such as osteoporosis. An inbred mouse strain provides a useful model for exploring environmental influences due to the ability to generate animals with a high level of genetic similarity. Two different inbred mouse strains with known differences in skeletal phenotypes, C57BL/6J (B6) and DBA/2J (D2), were exposed to two different methods of mechanical loading. An aerobic based exercise intervention, treadmill running, and a more resistance based intervention, tower climbing. We hypothesized there would be a differential skeletal response relative to exercise type within each strain.

METHODS

Ninety 180 day old female mice equally divided between B6 and D2 inbred strains were exposed to treadmill running, tower climbing or served as controls (15 in each group). The treadmill runners were put onto a rodent treadmill 5 days per week for 5 weeks and the speed, incline and duration were gradually increased. During the final week, a target speed of 15 m/min at a 25 degree incline for 30 minutes was reached. The tower climbers were housed in a cage attached to a 4 ft tall mesh wire tower with water bottles placed at the top of the

tower. Tower climbers remained in the towers 24 hours per day for a 5 week period. To train the mice during the first week, the water bottles were put at the bottom of the tower and gradually raised to the top. The mice then climbed to the top of the towers to drink for the remaining weeks of the intervention. The mice were sacrificed two hours after the last day of exercise and the right femur was harvested and frozen at -20C until tested. All procedures complied with and were approved by the Pennsylvania State University Institutional Care and Use Committee. After taking several gross morphological measurements, the cortical mid-shaft was evaluated prior to mechanical testing using micro-computed tomography (Scanco Medical, Zurich, Switzerland). The femur was then loaded to failure in three-point bending and the femoral neck was loaded to failure in a shear test using a MTS 858 Mini-Bionix apparatus (MTS Systems, MN, USA). Structural properties were derived from the load-displacement data. Material properties were estimated using the resulting cross-sectional and structural data. An ANOVA was used to evaluate the effects of exercise type within each strain on all structural, material and morphological variables. A 2-sided Dunnett was used for post hoc multiple comparisons. Significance was determined using a 95% confidence level.

RESULTS

We were primarily interested in the effects of exercise treatment within each strain. The B6 mice displayed numerous treatment effect differences. Treadmill running resulted in significantly greater values for load at yield, shear ultimate load (of the femoral neck) and cortical thickness at the lateral mid-diaphysis (Table 1). Tower climbing resulted in significantly greater values for head diameter, displacement at yield and strain at yield (Table 2). Both treadmill running and tower climbing significantly increased work to yield in the B6 mice as well. However, controls had significantly higher

values when compared to tower climbers for displacement, work, and strain at ultimate load as well as post yield displacement and post yield work at ultimate load and post yield displacement at failure. There were also significant differences between the control mice and the treadmill runners for coronal width and medullary area within the D2 strain with treadmill runners having smaller values than the controls. D2 mice also had significant differences for shear ultimate load and work with control mice having larger values than the tower climbers.

Table 1: Treadmill Running Effects for B6 Mice. Mean, standard error (SE) and significant p-values for Treadmill versus Control are shown.

Treadmill Effect for B6 Mice		Treatment	
Variable	Values	Treadmill	Control
Load at Yield (shaft)	Mean	12.944	11.515
	SE	0.459	0.347
	p-value	0.054	
Work to Yield (shaft)	Mean	0.713	0.582
	SE	0.040	0.024
	p-value	0.049	
Load at Ultimate (neck)	Mean	17.063	15.502
	SE	0.455	0.452
	p-value	0.044	
Cortical thickness at lateral mid-dipahysis	Mean	0.651	0.630
	SE	0.005	0.006
	p-value	0.020	

Table 2: Tower Climbing Effects for B6 Mice. Mean, standard error (SE) and significant p-values for Tower versus Control are shown.

Tower Effect for B6 Mice		Treatment	
Variable	Values	Tower	Control
Strain at Yield (shaft)	Mean	0.019	0.017
	SE	0.001	0.000
	p-value	0.022	
Work to Yield (shaft)	Mean	0.742	0.582
	SE	0.049	0.024
	p-value	0.014	
Displacement at Yield (shaft)	Mean	0.103	0.092
	SE	0.003	0.002
	p-value	0.019	
Head Diameter	Mean	1.526	1.464
	SE	0.010	0.016
	p-value	0.022	

DISCUSSION

These results provide further evidence that genetic background imparts differences in the response to mechanical stimuli. Differential intervention effects across the two inbred strains were confirmed, with B6 mice being more responsive than D2 mice. Both types of exercise had a positive effect on yield mechanical properties in the B6 mice. Treadmill running increased load at yield and work to yield at the mid-diaphysis and the load at ultimate load was also increased at the femoral neck. Tower climbing increased displacement at yield, work to yield and strain at yield at the mid-diaphysis. These results indicate a beneficial skeletal response to exercise within the B6 strain.

Strain and exercise type had an effect on skeletal morphology as well. Tower climbers within the B6 strain had significantly larger head diameters, demonstrating a positive skeletal response to the more resistance type of exercise intervention. Treadmill running increased the cortical thickness at the lateral mid-diaphysis within the B6 mice and decreased the medullary area in the D2 mice (indicating increased endocortical bone formation). Thus, aerobic based exercise resulted in positive morphological changes within both strains. The coronal width in the D2 mice, however, was less in the treadmill runners as compared to the controls.

Tower climber values were less at ultimate load than the controls for mechanical properties of the femoral mid-diaphysis within the B6 mice and of the femoral neck within the D2 mice. These results suggest that tower climbing may inhibit the maximum mechanical capacity at both the mid-diaphysis and femoral neck depending on strain. In summary, within the B6 strain, exercise positively increased yield mechanical properties at the mid-diaphysis, ultimate mechanical properties at the femoral neck and morphological parameters at both the mid-diaphysis and neck. Treadmill running also positively affected bone formation at the mid-diaphysis within the D2 mice.

CONCLUSION

These data provide evidence that there are skeletal responses to exercise relative to genetic strain and treatment type in adult mice.