Female Mice with Osteogenesis Imperfecta Exhibit Diminished Response to Tibial Compression Compared to Wild-Type Controls

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Introduction

Osteogenesis imperfecta (OI) is a disease of poor bone quality and increased fracture risk due to mutations in collagen and its processing proteins[1].

Load bearing exercise may improve bone structure in mild to moderate OI patients, but it is uncertain if patients will have a robust response to mechanical stimuli.

OI mice previously exhibited an impaired skeletal response to exercise, partly due to diminished muscle function[2]. Targeted mechanical stimuli can isolate skeletal responses to load.

Hypothesis: That targeted mechanical loading will improve bone structure and increase fracture resistance of the G610C mouse model of OI

References: [1]Forlino. 2016. Lancet. 387(10028): 1657–1671. [2]Gremminger et al. 2019. JBMR. 34(9):1646-1659.

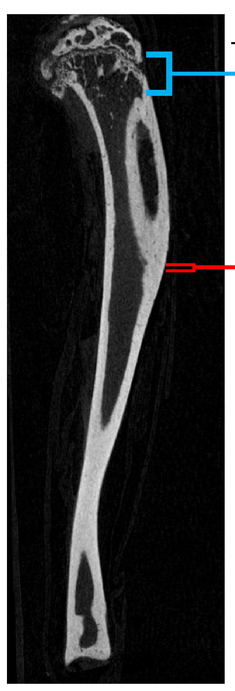
Study Design

Female G610C mice (G610C, n=5) and wild-type mice (WT, n=5) were subjected to in vivo axial compressive loading on the right tibia for 6 weeks starting at 10 weeks of age. Loading force was set to engender a strain of 1390 με in the mid-diaphysis (50% length). Left tibiae were used as non-loaded controls.

Tibiae were scanned with micro-computed tomography (9.8 μm voxel). Trabecular and cortical bone structure were determined.

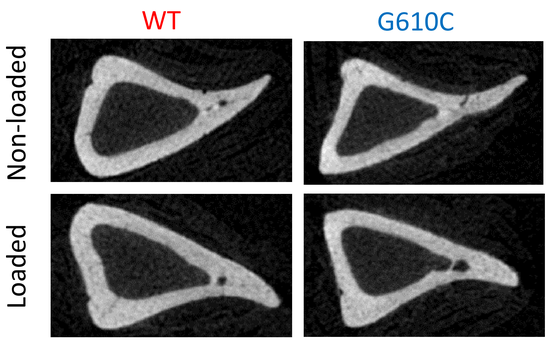
Two way repeated measures ANOVA determined the effect of loading and genotype. Multiple comparisons were done with Sidak's post-hoc tests when interaction terms were significant.

Tibial compression
Main et al. Journal of Orthopaedic Research. 2020.

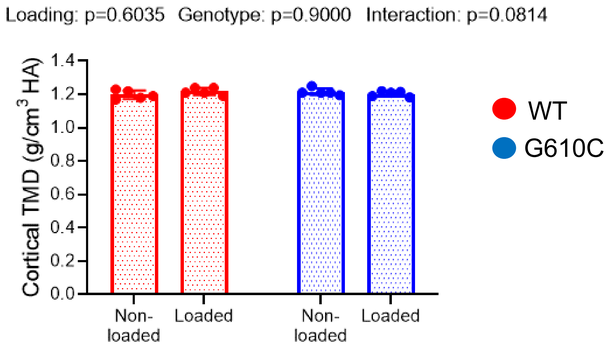


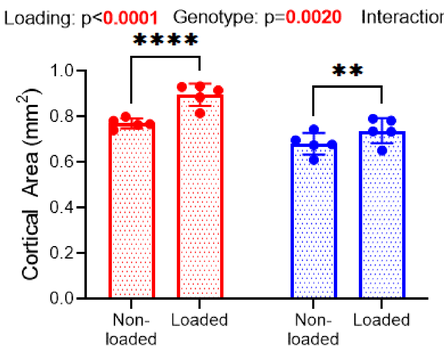
Microcomputed tomography image with regions of interest

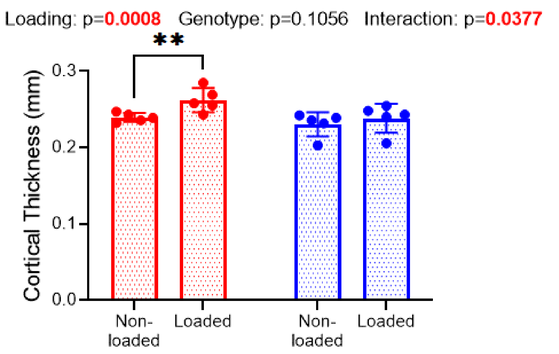
Cortical area increased with loading in both genotypes, but cortical thickness only increased with loading in WT mice



Representative cortical bone images



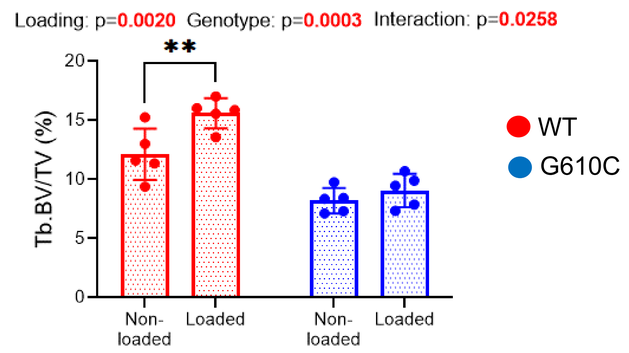


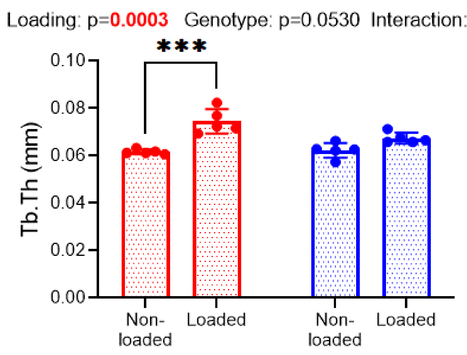


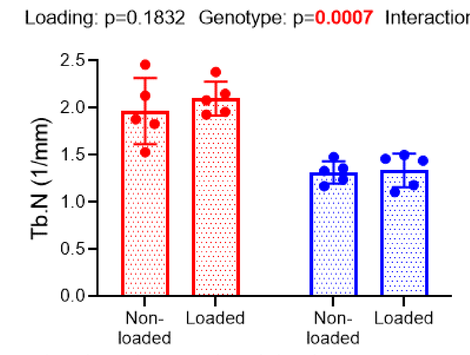
Cortical bone parameters tissue mineralization density (TMD), area, and thickness. Two way ANOVA values are listed above graphs. Asterisks indicate significant differences with multiple comparisons with ** = p<0.01 and **** = p<0.0001

Trabecular bone volume increased with loading in WT mice, but not G610C mice

Representative trabecular bone image with ROI







Trabecular bone volume fraction (Tb.BV/TV), trabecular thickness (Tb.Th), and trabecular number (Tb.N). Two way ANOVA values are listed above graphs. Asterisks indicate significant differences with multiple comparisons with ** = p<0.01 and *** = p<0.001

Discussion

- OI mice were able to build bone in response to mechanical loading, but the response was less robust compared to WT controls
- Increased trabecular bone volume with loading was due to increased trabecular thickness, whereas differences in genotypes were due to lower trabecular number
- Impaired cortical bone response could be due to decreased osteoblastogenesis or an impaired response of the osteocyte to sense loads

Conclusion: OI mice formed bone in response to loading but had a diminished response. Future work is needed to determine the mechanism of diminished bone response and quality of formed tissue.

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