EFFECTS OF ZOLEDRONATE AND MECHANICAL LOADING DURING SIMULATED WEIGHTLESSNESS ON BONE STRUCTURE AND MECHANICAL PROPERTIES

R. T. Scott[1], M. O. Nalavadi[2], Y. Shirazi-Fard[4], A. B. Castillo[3], and J. S. Alwood[4]
[1]San José State University, San Jose, CA, [2]Santa Clara University, Santa Clara, CA, [3]New York University, Brooklyn, NY, and [4]Space Biosciences Research Branch, NASA Ames Research Center, Moffett Field, CA.

Space flight modulates bone remodeling to favor bone resorption. Current countermeasures include an anti-resorptive drug class, bisphosphonates (BP), and high-force loading regimens. Does the combination of anti-resorptives and high-force exercise during weightlessness have negative effects on the mechanical and structural properties of bone? In this study, we implemented an integrated model to mimic mechanical strain of exercise via cyclical loading (CL) in mice treated with the BP Zoledronate (ZOL) combined with hindlimb unloading (HU). Our working hypothesis is that CL combined with ZOL in the HU model induces additive structural and mechanical changes.

Thirty-two C57BL/6 mice (male, 16 weeks old, n=8/group) were exposed to 3 weeks of either HU or normal ambulation (NA). Cohorts of mice received one subcutaneous injection of ZOL (45µg/kg), or saline vehicle, prior to experiment. The right tibia was axially loaded in vivo, 60x/day to 9N in compression, repeated 3x/week during HU. During the application of compression, secant stiffness (SEC), a linear estimate of slope of the force displacement curve from rest (0.5N) to max load (9.0N), was calculated for each cycle once per week. Ex vivo µCT was conducted on all subjects. For ex vivo mechanical properties, non-CL left femurs underwent 3-point bending.

In the proximal tibial metaphysis, HU decreased, CL increased, and ZOL increased the cancellous bone volume to total volume ratio by -26%, +21%, and +33%, respectively. Similar trends held for trabecular thickness and number. Ex vivo left femur mechanical properties revealed HU decreased stiffness (-37%), and ZOL mitigated the HU stiffness losses (+78%). Data on the ex vivo Ultimate Force followed similar trends. After 3 weeks, HU decreased in vivo SEC (-16%). The combination of CL+HU appeared additive in bone structure and mechanical properties. However, when HU + CL + ZOL were combined, ZOL had no additional effect ($p>0.05$) on in vivo SEC. Structural data followed this trend with ZOL not modulating trabecular thickness in CL + NA/HU mice.

In summary, our integrated model simulates the combination of weightlessness, exercise-induced mechanical strain, and anti-resorptive treatment that astronauts experience during space missions. Based on these results, we conclude that, at the structural and stiffness level, zoledronate treatment during simulated spaceflight does not impede the skeletal response to axial compression. In contrast to our hypothesis, our data show that zoledronate confers no additional mechanical or structural benefit beyond those gained from cyclical loading.

Supported by a NASA Space Biology New Investigator Award (NNH12ZTT001N).