Site-Specific Protection against Disuse-Induced Bone Loss in Rats Treated Prophylactically with Zoledronic Acid and High-Impact Loading

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Disclosures:

Introduction: Recent data from the International Space Station reveal a promising effect of bisphosphonates (BPs) taken before and during in-flight missions (1). Compared to controls, declines in bone mineral density in the femur and spine were drastically reduced with BP treatment. Although the data are encouraging, confounding factors in the control groups (i.e., use of different exercise equipment within the cohort) exist and make interpretation of these results challenging. Thus, the combined role of BP and exercise remains unclear. Previous rodent studies from our lab reveal a hindrance of bone formation when a BP was used in combination with exercise (2). In the current study, high-impact simulated exercise was administered prior to, rather than following, BP administration. We hypothesized that this novel sequential pretreatment would protect against disuse-induced bone loss. We further conjectured that the sequential combination of simulated exercise and BP pretreatment would protect better than either treatment alone.

Methods: Seventy-two male Sprague-Dawley rats (5.5-mo-old) were block assigned based on initial body weight to one of six groups (n=12): BC (baseline control), CC (cage control), HU (hindlimb unloading), ZA+HU (Zoledronic Acid prior to HU), SE+HU (simulated exercise prior to HU), and SE+ZA+HU (simulated exercise followed by ZA prior to HU). SE took place 3x/wk and consisted of 25 high-impact, free-fall drops per session from a height of 60 cm for 5 weeks (35d). A single-dose of ZA (60 µg/kg body weight) was administered following SE and just prior to HU. HU for 28d was achieved via the traditional tail suspension method. In vivo peripheral quantitative computed tomography (pQCT) scans were performed on days 0, 35, and 65 at the proximal tibia metaphysis (PTM) and ex vivo micro computed tomography (µCT) was conducted at the distal femur metaphysis (DFM).

Results: When normalized to body weight, 35d of SE increased total vBMD (9.5%) and cortical vBMD (9.5%) and decreased cancellous vBMD (-8.5%) at the PTM. HU caused a marked decline in PTM total vBMD (-10.0%), cortical vBMD (-8.9%) and cancellous vBMD (-20.6%) compared to baseline. There was a main effect of ZA therapy: animals treated with ZA were protected against disuse-induced PTM bone loss evidenced by sustained levels of vBMD (total, cortical, and cancellous) during HU. SE alone, however, did not protect the PTM from bone loss. Further, there was no additive/synergistic effect of combining SE with ZA at the PTM. At the DFM, however, µCT revealed that both ZA and RE alone prevented bone loss, whereas SE+ZA was the most beneficial (Figure 1).

Discussion: Our study demonstrated that the prophylactic treatment of ZA was capable of preventing HU-induced bone loss in the PTM and DFM of skeletally mature rats. Although SE was anabolic to bone prior to HU, it was unable to prevent losses during unloading in the PTM. µCT results, however, demonstrated that the combination of ZA with SE was better than either treatment alone. Altogether, this is the first study to document protection from disuse bone loss in rats via ZA and/or simulated exercise. Future studies may seek to explore the effect of exercise administered before and during HU, alone and in combination with ZA, to better simulate how the combination treatment could benefit crew members on long duration space exploration.

Significance: Because of the adverse side effects of oral bisphosphonates, NASA is currently considering the use of the injectable ZA in its long-duration crew members. Results from this study demonstrate, for the first time in the rat model, that a single injection of ZA is capable of preventing disuse-induced bone loss. These data have profound applications for astronauts as NASA aims to explore farther into outer space than ever before.

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2. Swift JM, Swift SN, Nilsson MI, Hogan HA, Bouse SD, and Bloomfield SA. Cancellous bone formation response to simulated resistance training during disuse is blunted by concurrent alendronate treatment. Journal of bone and mineral research : the
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Relative Bone Volume

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<th></th>
<th>CC</th>
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