Effects of Parathyroid Hormone Treatment in Ovariectomized Rats

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INTRODUCTION:

Bone’s resistance to fracture is not only influenced by its mass, but also by its material properties. These properties can be altered by pathologies such as post-menopausal osteoporosis due to the withdrawal of estrogen. Intermittent parathyroid hormone (PTH) treatment stimulates osteoblasts and increases bone formation [1]. Although osteoblast activation also instigates osteoclastogenesis, the overall effect of PTH therapy is shown to increase bone mineral density and decrease fracture risk in post-menopausal osteoporotic patients [2]. The ovariectomized (OVX) rat is a the standard model for testing the efficacy of osteoporosis therapies as OVX simulates a postmenopausal state by depleting estrogen levels and accelerating bone loss. OVX in rats may also result in a loss of bone mineral, ultimately leading to increased fracture risk [3]. Here, our goal was to use a novel fracture mechanics approach to measure the fracture toughness of cortical bone and investigate the influence of PTH on bone’s material properties in the OVX rat.

METHODS:

36 female Sprague-Dawley rats were divided into untreated OVX and OVX+PTH treated (3 doses) rats. OVX was performed out at 5 months of age. Treatment was started at 6 months with high, medium, or low doses of PTH (75 µg/kg, 15 µg/kg, 0.3 µg/kg, respectively). Rats were sacrificed at 12 months.

Cortical microbeams (0.70 x 0.85 x 11.3 mm) from the lateral quadrant of one femur were cut using a diamond blade saw. Uneven surfaces were polished down using fine grit sandpaper. Microbeams were notched similar to ASTM standards using a scalpel blade on the periosteal side to approximately 20% of the width [4]. The span length was fixed at 3.2 mm. They were tested via 3-point bending fracture toughness tests at 0.001 mm/s until failure under constant hydration with saline [4,5] using a micro-mechanical testing system (EnduraTEC ELF3200).

Micro-computed tomography was used to measure bone geometry prior to testing and to measure maximum stable crack length after testing. Force-deformation curves, specimen geometry, and notch parameters were used to calculate initiation toughness ($K_{ini}$) and propagation toughness ($K_{prop}$). Fracture toughness values were compared between all experimental groups and controls using One-Way ANOVA and t-tests.

RESULTS:

Microbeams had an average of 1.74 times higher $K_{prop}$ (1.84 ± 0.42 MPa/m) than $K_{ini}$ (1.06 ± 0.44 MPa/m, p<0.01). One-Way ANOVA for initiation toughness showed no significant difference between OVX (n=8) and all PTH-treated groups. One-Way ANOVA with Student-Newman-Keuls post-hoc test showed a significant difference between OVX and PTH-treated groups (p<0.001) with specific differences between high dose PTH and low dose PTH (p<0.05, Figure 1) as well as between OVX and low dose PTH (p<0.05, Figure 1).

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Table 1. The propagation toughness for PTH treated groups is shown as (top) the percent decrease of the group compared to OVX rats, and (bottom) the sample size per group.

DISCUSSION:

As PTH has been shown to increase bone mass and decrease fracture risk [2], it was hypothesized that its administration on OVX rats would increase bone’s fracture toughness in OVX rats. However, our results show that when compared to OVX controls, low dose of PTH significantly reduces bone toughness and high doses have no significant effect. The absence of improvement in PTH treated cortical bone toughness may be associated with the differential effects of PTH on cortical versus cancellous bone. In particular, studies on rats suggested that PTH primarily increases BMD in trabecular bone via increased bone formation while it increases BMD in cortical bone via increased mineral apposition because of limited remodeling [6]. Increased mineralization can increase brittleness and reduce bone fracture toughness in the low dose PTH group as was found in our study. Furthermore, limited remodeling of cortical bone may cause changes to the bone matrix including the formation of post-translational modifications of collagen and alterations in non-collagenous protein content.

SIGNIFICANCE:

Anabolic treatments such as PTH are commonly used as osteoporosis treatments. This study investigates the effect of PTH on cortical bone fracture toughness in ovariectomized rats.

ACKNOWLEDGMENTS:

Funding was provided by NIH-NIAMS AR052778 and NIH-NIGMS T32GM067545.

REFERENCES: