2017 Abstracts

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MO0401

Age–related changes in the anabolic response to exercise. Niloufar Rostami*, Chunbin Zhang, Joseph Gardinier. Henry Ford Hospital, United States

Exercise is a key determinate of fracture risk and is often used to promote bone formation through dynamic loading. However, the efficacy of exercise to stimulate bone formation is often lost with age. The purpose of this study was to identify age-related differences in the response to exercise at the tissue and cellular level. The hypothesis states that osteocytes' response to exercise is diminished with age alongside the adaptation in tissue strength. Young (8-weeks of age) and old (36-weeks of age) male mice were weight-matched and assigned to baseline, sedentary and exercise groups with 20 mice per group. Exercise involved 30 minutes of treadmill running on 5° incline at speed of 12 m/min each day under approval by Henery Ford Health System Institutional Animal Care and Use Committee. After 6 days exercise, 5 mice from each group were sacrificed to measure early changes in gene expression based on qRT-PCR analysis of the tibia. The remaining mice from each group were sacrificed after 5 weeks of exercise to measure changes in the mechanical strength of the tibia alongside protein expression based on immunohistochemistry and serum analysis. At the cellular level, osteocytes' expression of sclerostin was significant reduced during exercise in young mice based on mRNA expression by day 6 (0.64±0.08 vs. 1.0±0.12, $<0.05p$) and immunohistochemistry after 5 weeks of exercise. However, serum analysis of young mice did not reflect a decrease in circulating levels of sclerostin (182±30.8pg/ml vs. 161±23.8pg/ml, $>0.4p$). In aged mice, exercise had no effect on osteocytes' gene or protein expression of sclerostin. As expected, 5 weeks of exercise in young mice increased the ultimate load of the tibia compared with sedentary controls (20±2.97N vs. 18±2.5N, $<0.007p$), along with the post-yield deformation (440.5±328.1μm vs. 259.2±152.1μm, $<0.04p$). Despite significant differences in mechanical behavior, exercise in young mice had no effect on bone growth based on cortical area (0.71±0.051mm^2 vs. 0.74±0.08mm^2, $>0.2p$) and moment of inertia (0.082±0.012mm^4 vs. 0.085±0.018mm^4, $>0.6p$). In contrast, exercise in older mice had no significant effect on bone strength, but prevented age-related bone loss that was evident in sedentary mice when compared to baseline (0.67±0.03 vs. 0.75±0.06, $<0.05p$). Overall, these data suggest that osteocytes age-related differences in osteocytes' capacity to suppress sclerostin levels during exercise may explain the inefficacy of exercise to improve bone strength in aged mice.

Disclosures: Niloufar Rostami, *None.*

MO0402

Finite Element Models of Linear Microcracks in Trabecular Bone with Simulated Bisphosphonate and Raloxifene Treatment. Max Hammond*[1], Joseph Wallace[2], Matthew Allen[3], Thomas Siegmund[1]. [1]Purdue University, United States, [2]Indiana University - Purdue University Indianapolis, United States, [3]Indiana University School of Medicine, United States

At the nanoscale bone is composed of aligned heterogeneously mineralized collagen fibrils. While raloxifene (Ral) and bisphosphonate (BP) treatment preserve bone mass, they also affect bone quality through changes in collagen hydration and mineral density/heterogeneity, respectively. It was hypothesized that the effects of pharmacological treatment on the tissue would alter linear microcracking in finite element (FE) models of trabeculae reflecting control (Ctrl), Ral and BP.

A FE mesh of a single canine vertebral body trabecula was generated from a micro-CT scan using ScanIP. A custom MATLAB code imposed tissue property heterogeneity and a collagen fibril orientation parallel to the trabecular surface. Ctrl was heterogeneous (based on vBMD) in both modulus and strength, and BP was homogenous (+25% of Ctrl mean modulus and strength). Ctrl and BP models had identical microcracking toughness. Ral had increased microcracking toughness (+25%) and the same modulus and strength heterogeneity as Ctrl. Transverse deflections were applied to simulate bending of the trabeculae, microcrack formation and propagation was simulated with the imposed orientation using the extended FE method in Abaqus/Standard, and the energy dissipated by the microcrack was assessed.

In all models microcracks initiated in the trabecular interior, and microcrack surfaces were aligned with collagen orientation. Therefore, the model correctly predicts the linear microcrack formation commonly observed in trabecular bone due to loading. Predicted deflection at crack initiation was similar for all models (BP at 7.3 μm; Ctrl and Ral at 7.2 μm). Microcracks advanced little until 9 μm deflection, after which microcracks grew rapidly (Fig. 1). At 10 μm deflection, the energy dissipation for BP was 2.5x greater than Ctrl, whereas there was no difference between Ctrl and Ral. Considering a constant energy dissipation value, Ctrl and Ral sustained about 15% more displacement than BP. The differences between BP and Ctrl demonstrate the important contribution of heterogeneity to resisting microcrack propagation. The present method automatically applied heterogeneity and orientation based on CT data. Therefore, the technique is readily scalable to model bone fragility and microdamage in larger trabecular samples and could use other data that estimates 3D geometry and mineral density (e.g., in vivo HRpQCT). In conclusion, altered microcracks were predicted with bisphosphonate but not raloxifene models.

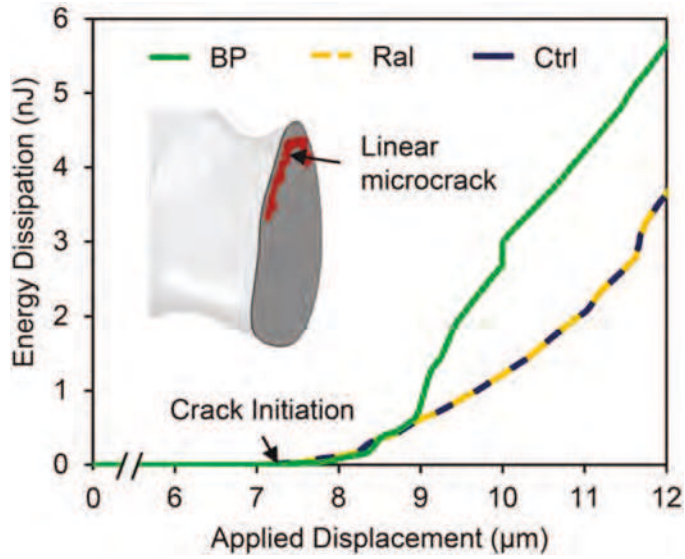

Figure 1: Predicted energy dissipation from microcracking was altered in the bisphosphonate model

Disclosures: Max Hammond, *None.*

MO0403

Fracture toughness and geometry-independent microscale material properties are improved with exercise for male but not female rats in diet-induced obesity. Chelsea Heveran*[1], Rebecca Foright[2], Ginger Johnson[2], Virginia Ferguson[1], Paul MacLean[2], Vanessa Sherk[2]. [1]Department of Mechanical Engineering, University of Colorado, United States, [2]Department of Medicine, Division of Endocrinology, Metabolism & Diabetes, University of Colorado Anschutz Medical Campus, United States

Obesity increases bone fracture risk, yet combined effects of obesity, exercise, and sex differences on fracture toughness (K_c) are not understood. This study assessed whether diet-induced obesity (DIO) impairs K_c and microscale bone quality, and whether exercise can mitigate negative effects of DIO. The study also tested whether DIO and/or exercise are sex-specific.

Female and male Wistar rats (N = 31) were fed an ad libitum high fat diet (HFD) for 10 weeks, starting at 5 weeks of age. Within sex, obese and lean groups were defined as the highest and lowest tertiles of weight and fat gain. Obese and lean rats were randomized to exercise (EX) or sedentary (SED) controls for the last 4 weeks of HFD (n = 4/group; except female obese EX: n = 3). EX was treadmill running at 15 m/min, 60 min/day, 5 days/week.

K_c was evaluated in notched femurs. Post-fracture, femurs were dehydrated, embedded, and polished to a 0.1 μm finish. Nanoindentation was performed with 25 indents each for lamellar and woven bone in the medial quadrant. Nanoindentation modulus (E) and plastic work (W, hysteresis of unloading curve) were averaged per lamellar/woven region. Three-way ANOVA evaluated how K_c, E, and W depended on sex, obesity status, and exercise status.

Bone radii and thickness were 36.0% ($p < 0.01$) and 28.5% ($p < 0.01$) larger, respectively, in males than females but did not differ with exercise or obesity. Male lean EX rats had 21% tougher (*i.e.,* higher K_c) bone than male lean SED ($p = 0.05$). Male obese EX rats had 22% tougher bone than male obese SED ($p = 0.04$). Female rats had less tough bone than males (-12.6%, $p = 0.05$), and did not improve K_c with exercise.

Diminished K_c in SED males corresponded to decreased microscale bone material quality, but the location of lower quality bone depended on obesity status. Obese SED rats may have lower E in woven bone compared with obese EX (-9.1%, $p = 0.07$). Lean SED rats may have lower W in lamellar bone compared with lean EX (-13.0%, $p = 0.06$). For all lean EX rats, increased heterogeneity (*i.e.,* variance) of E in lamellar bone correlated with greater K_c ($r^2 = 0.57$). Meanwhile, variance in E did not change Kc in obese or SED rats.

In summary, K_c was preserved with EX for both lean and obese male rats fed HFD, but not for females. Lower K_c in male SED rats corresponded with decreased microscale bone quality. These findings may help explain the effects of sex and exercise on obesity-related bone fragility.