Multi-scale Investigation of Weight-bearing Exercise on Bone Biomechanical Integrity in the Osteogenesis Imperfecta Model (*oim*) Mouse.

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Osteogenesis imperfecta (OI), a heritable connective tissue disorder generally due to type I collagen defects, is characterized by small stature, reduced bone mineral density, and frequent fractures. Bone is inherently mechanosensitive, responding and adapting to its mechanical environment. Bone formation occurs in response to high mechanical loads; often changing its geometry to strengthen the skeleton. In humans, during the normal 2 year prepubertal/pubertal growth period normal children attain 26% of their peak bone mass, and children which are physically active accrue 10-40% more bone (region specific) than inactive children. This suggests that sedentary lifestyle choices of children with OI are particularly detrimental to their bone health. We postulate that even though the OI bone material is biomechanically weaker, the OI bone will respond to exercise (muscle loading and/or gravitational ground force), especially during pubertal growth by altering bone geometry, architecture, and/or mineral:matrix physiochemistry to generate an inherently stronger bone. The potential benefits of therapeutic exercise to OI patients are significant, but the risks are real. It is critical that we first demonstrate the feasibility and potential success of an exercise therapy in a mouse model of OI for it to be considered a viable therapy for patients.

To address this need we combined the unique strengths of two University of Missouri Campuses (Columbia and Kansas City) to create a collaborative research team from the Departments of Biochemistry (UMC) and Veterinary Pathobiology (UMC) and Oral Biology (UMKC School of Dentistry) to determine if weight bearing exercise will improve bone biomechanical integrity in a mouse model of osteogenesis imperfecta (*oim*), and to investigate the molecular, biochemical, physiochemical, structural and biomechanical impact of exercise on

bone at the macro-, ultra- and nano-structural levels. The relationship of whole bone biomechanical integrity and geometry to the mineral:matrix composition, architecture, crystal geometry, and the matrix:mineral interactions of bone is poorly understood. Therefore, we examined femurs of wildtype and *oim* mice by multi-scale analyses characterizing geometry (μCT) and biomechanics (torsional loading to failure) in relation to the bone mineral and matrix, physicochemical and mechanical properties (FTIR, Raman and scanning acoustic microscopy). By μCT and torsional loading to failure we defined the geometric structural properties and the whole bone biomechanical properties (torsional ultimate strength, torsional stiffness, and strain energy until failure), which are a function of both the geometry and bone biomechanical material properties (tensile strength and shear modulus of elasticity). We used FTIR and Raman microscopy in conjunction with scanning acoustic microscopy to correlate the chemical structure and composition with mechanical integrity. We then performed the same analyses on femoral bones from wildtype and *oim* mice that underwent moderate weight bearing exercise (running on a treadmill) to determine if weight bearing exercise could alter the molecular structure of bone mineral:matrix and improve bone physicochemical and biomechanical properties. Our preliminary findings support the hypothesis that weight bearing exercise induces an adaptive response in *oim* mouse bone to alter its matrix/mineral composition, physiochemical structure/property, and geometry to increase bone quality and biomechanical strength.