Mechanisms of bone fragility with skeletal growth in osteogenesis imperfecta

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In classical osteogenesis imperfecta (OI or *brittle bone disease*) mutations in the genes encoding collagen type I alter collagen structure resulting in bone fragility [1]. We showed that bone fracture resistance is low in the homozygote *oim* mouse model of OI [1], already at a very young age, with bones getting tougher as the mouse grows and matures [2]. The mechanisms by which OI bone resists fracture varies with skeletal growth. Crack path examination showed for the first time the presence of crack deflections, splitting, and bridging in young (4 w.o.) *oim* bones, but not in more mature (14 w.o.) ones [2]. These are toughening mechanisms usually observed in healthy bone. Young *oim* mouse bone showed low resistance to fracture even before the crack forms but not while it grows, while mature *oim* mouse bone exhibited low toughness during crack grow but not at crack initiation. To determine the mechanisms of bone fragility in *oim* bones at these stages of skeletal growth, and explain the observed differences in fracture toughness, we here examine changes in the *oim* bone tissue structure and composition at different ages. We assessed *oim* bone intracortical porosity with synchrotron microtomography, quantified collagen composition, fibers orientation and organization in *oim* bones using second harmonic generation microscopy, and determined bone tissue composition, and the presence of advanced glycation end products (AGEs) using Raman spectroscopy and molecular fluorescence.
Compared to mature *oim* bone, young *oim* bone tissue exhibit high lacunar porosity density, low collagen content, disorganized mineralized fibers with low carbonate substitution and mineral crystallinity, and high CML/CH2-wag and florescent AGEs. These parameters describe a poorly organized bone tissue in young *oim* mice that can explain their lower fracture resistance compared to mature bone. Cracks favorably initiate in presence of defects, such as lacunae porosity, and in tissue with low plasticity due to poor collagen and mineral properties and interaction. Furthermore, the increased number of AGEs per collagen content, together with the reduced collagen content, further underlines the controversial role that non-enzymatic crosslinks could possibly have in oim bones. This study suggests that treatments for OI bone fragility should differ in young and mature populations, targeting two different mechanisms of bone fragility.

1. A. Carriero, et al., JBMR. 29:6, 2014
2. A. Docaj, et al., ASBMR, 2020