Bone toughness changes during skeletal growth in brittle osteogenesis imperfecta bone. How? and why?

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Background
There is no cure for osteogenesis imperfecta (OI). To develop new effective treatment strategies for their bone fragility. it is of paramount importance to know how OI bones fracture, if their mechanisms change with skeletal growth and how they relate to their bone properties. This study examines fracture toughness, related toughening mechanisms and collagen fiber orientation in the growing *oim* mouse model of OI.
Experimental Approach
Femora from 4- and 12-week-old (w.o.) B6C3fe-a/acolla2$^{oim/oim}$ (*oim*/*oim*) and their healthy (WT) counterparts (N=7-11/group) were notched and loaded in bending to characterize the toughness of OI bone during skeletal growth. These mouse ages are the human equivalent of 10 and 18 y.o. To identify the dominant sources of toughness and their contributions to the bone's resistance, R-curves were plotted, and crack path examined to identify the presence of toughening mechanisms. Collagen fiber orientation has been investigated in tibial mid-diaphyseal cross-sections of WT and *oim*/*oim* mice at their forth quadrants (anterior, posterior, medial and lateral side) using second harmonic generation (SHG) microscopy. Degree and distribution of orientation were determined as descriptors of collagen organization.
Data
Bone fracture toughness increases with skeletal growth in all mice. However, *oim/oim* bone has lower fracture toughness compared to WT at all age (67% and 50% decrease in the 4 and 12 w.o. mice, respectively). OI bones revealed a loss in crack extension, initiation and crack growth toughness compared to WT. Furthermore, 4 w.o. *oim/oim* bones had a lower initiation toughness and stable crack extension than 12 w.o. *oim/oim*, but higher crack growth toughness, which is actually ~2/3 of that of WT bone at the same age. Toughening mechanisms of crack deflections, splitting and crack-bridging were observed in WT bones at both ages and in 4 w.o. *oim/oim* bone while they were absent in 12 w.o. *oim/oim* bone. At this age WT bone showed organized collagen fibers oriented parallel to the periosteum and endosteum surfaces, while the *oim/oim* bone mostly has a disorganized micro-lamellar organization with inconsistent orientation. This is in agreement with the lower fracture growth observed at this age.
Conclusions
This study shows for the first time the presence of toughening mechanisms in very young *oim/oim* bone that are absent in more mature *oim/oim* bone, where bone has however twice as much toughness. Changes in bone tissue structure, composition and intracortical porosity must be naturally occurring during skeletal growth. Our findings have implications for developing targeting clinical therapies for OI bone fragility at different ages.