Long-term alendronate does not improve bone fracture resistance in osteogenesis imperfecta mice

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Osteogenesis imperfecta (OI) or brittle bone disease is a genetic disorder occurring in 1/10,000 human births. It is caused by bone fragility and skeletal deformities due to mutations in the collagen type I. OI has no cure, and current treatments rely primarily on bisphosphonates, a class of antiresorptive drugs, aiming to enhance bone mass in children with OI. Controversial are the results related to bisphosphonates as if it can rescue bone fragility in OI. As bone fracture is the primary symptom of OI, it is crucial to understand how this drug treatment affects the bone resistance to fracture. In this study, we investigate whether long-term use of alendronate is effective in improving bone fracture toughness (i.e. bone resistance to fracture) in brittle OI bones from the *oim* mice. Sexual dimorphism is assessed. We also characterized the mechanical environment on bone during loading and crack progression using digital image correlation system.

Femurs of 14-week-old alendronate-treated (ALN 0.21 mg/kg/week, 0.1 ml/1g BW starting at 2 weeks of age) and saline control (CTR) B6C3fe-a/acol1a2$^{oim/oim}$ (*oim/oim*) and wild-type (WT) mice (N=5/group/sex) were notched, surface speckled, and tested in 3-point bending for fracture toughness (at 0.01 mm/s) while 2 CCD cameras (100 mm focal lenses) recorded images of the crack growth on the external bone surface at 22 Hz. Bone surface strains were calculated by Aramis SRX System (GOM) during the crack growth. Following the mechanical test, bone fracture surfaces were imaged in back-scattered mode in an ESEM (Zeiss Supra 55) and bone fracture toughness was calculated. A statistical analysis was conducted to discern significant differences between groups and between sexes.

Oim/oim CTR bones exhibited a drastic decrease in fracture toughness compared to WT CTR bones. ALN treatment did not improve *oim/oim* bone fracture resistance, and actually significantly reduced the fracture toughness of WT bone. The stable crack growth extension was smaller in *oim/oim* vs. WT bones, with/out treatment. Similarly, it was smaller in the *oim/oim* ALN-treated vs. *oim/oim* CTRL bones. Only WT bones exhibited crack deflections. WT bones resisted higher strains both ahead and behind the crack tip before fracturing in CTRL and ALN; however, ALN treatment reduced the maximum strain. Sexual dimorphism was observed in WT ALN-treated groups with bones from female mice showing higher fracture toughness vs. male counterparts.