EFFECT OF ALENDRONATE ON BONE FRACTURE TOUGHNESS IN OSTEOGENESIS IMPERFECTA

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INTRODUCTION

Brittle osteogenesis imperfecta (OI) bone has disorganized collagen matrix and abnormal mineralization [1], with reduced resistance to crack initiation and propagation [2]. OI has no cure, and current treatments rely primarily on the use of bisphosphonates, a class of antiresorptive drugs, to enhance bone mass. While bisphosphonates have been proven to increase bone mineral density and improve mobility in children with OI, its effect on the fracture rate and its long-term efficacy and safety use to treat OI children remains unclear and needs further research [3]. In this study, we analyze whether long-term use of alendronate is effective in restoring toughness in OI brittle bones. We further characterize the mechanical environment on bone during loading and crack progression using digital image correlation (DIC).

METHODS

Femurs from B6C3fe-a/acolla2$^{oim/oim}$ (*oim/oim*) mice model of OI, and wild type (WT) counterpart were considered for the characterization of the bone toughness and crack growth. Mice received either alendronate (ALN 0.21 mg/kg/week) or saline in equal volume of 0.1 ml/1g BW [4] starting at 2 weeks of age till sacrifice at 14 weeks. All mice (N=2-3/group) were male. Fresh frozen bones were machine-notched at their mid-diaphysis and immersed in PBS for 24 hrs. Bones were then covered with a thin layer of water-based white paint and speckled with acrylic black paint using a high precision airbrush. Femurs were tested in 3-point bending at a displacement rate of 0.01 mm/s till failure while two CCD cameras (100 mm focal lenses, GOM) recorded images at 32 Hz. Strains distributions engendered by load application were calculated by Aramis SRX System (GOM). Following mechanical testing, fracture surfaces of fully broken bones were imaged in back-scattered mode in an environmental scanning electron microscope (ESEM, Zeiss Supra 55) a Bone fracture toughness was calculated in terms of stress-intensity factor [5].

RESULTS

Oim/oim bones from our sample cohort exhibited a drastic decrease in fracture toughness compared to WT counterparts (Fig. 1). ALN treatment did not enhance *oim/oim* bone fracture toughness, and actually reduced the fracture resistance of WT bone. The extent of stable crack growth was decreased in *oim/oim* bone vs. WT ones, and was further reduced in ALN-treated bone. Only WT bone showed clear crack deflections. WT bones resisted higher strains both ahead and behind the crack tip before fracturing (Fig. 2). Major principal strains ahead of the crack tip were 5.9%, 2.4% for WT and *oim/oim* bone, respectively, and 1.9%, and 0.6% for their ALN-treated counterparts.

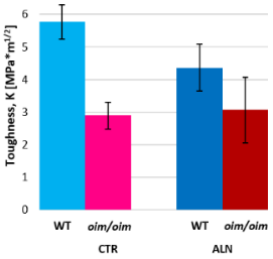

Figure 1: Bone fracture toughness of healthy (WT) and oim/oim mice treated with saline (CTR) or alendronate (ALN).

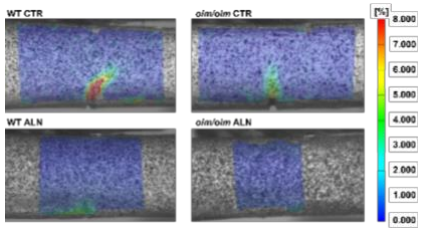

Figure 2: Major principal strain maps on the bone surface during loading at the full extent of the stable crack for saline (CTR) and ALN-treated WT and oim/oim bone. The red color covers a crack extent.

DISCUSSION

Results from this study suggest that the low fracture resistance of *oim/oim* bone is not improved following long term ALN treatment, although the increase in bone mass [4]. Full-field DIC principal strains, although only on the external bone surface, are able to predict the direction of crack growth, in both WT and *oim/oim* bones, with higher values for WT. A larger cohort of samples is currently being tested to statistically determine the effect of ALN on OI bone toughness and understand effects on their mechanical environment. Furthermore, bones from female mice are being examined to assess possible sexual dimorphism in responding to ALN therapy.

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Acknowledgments

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