

## Low-Dose Lithium Regimen Significantly Augments Rodent Osteoporotic Bone Fracture Healing

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**Purpose:** Osteoporotic bone fractures are highly prevalent and involve lengthy recovery. Lithium is a known anabolic agent for bone that inhibits glycogen synthase kinase-3 $\beta$  in the Wnt/ $\beta$ -catenin pathway, leading to upregulation of osteogenesis. Recently, we demonstrated that optimized lithium regimen (20 mg/kg LiCl from 7 days post fracture for 14 days) improve femoral fracture healing in healthy rats (46% higher torsional strength at 4 weeks). This study assessed lithium therapy to improve fracture healing in osteoporotic bone.

**Methods:** Three-month-old female Sprague Dawley rats were bilaterally ovariectomized and housed for 3 months to establish osteoporotic phenotype. Closed diaphyseal fractures were created in prestabilized femurs using a load drop apparatus. The optimal regimen for healthy rats (day 7 onset, 20 mg/kg oral dose, and 14 days duration) was evaluated against saline (control) treatment, with femurs harvested at 4 weeks. A second set of rats under a regimen with day 10 onset at the same dose and duration was evaluated with femurs harvested at 6 weeks. Femurs were  $\mu$ CT scanned at 14.8  $\mu$ m voxels and destructively tested under torsion. Maximum yield torque was the primary outcome measure. Student t tests were used to determine differences between the treatment groups and their respective controls. Pearson correlation analysis was performed between stereologic and biomechanical strength measures.

**Results:** Of the 49 fractured rats, 37 with fragmentary diaphyseal fractures were included. Onset at day 10 led to 50% higher maximum yield torque at 6 weeks (309 vs 206 N-mm,  $P=0.005$ ;  $n=7,7$ ). Treatment onset at day 7 suggested a trend toward a modest 13% improvement in maximum yield torque evaluated at 4 weeks (234 vs 206 N-mm,  $P=0.10$ ;  $n=10,13$ ). In paired comparisons of stereologic parameters to controls, the day 10 onset lithium group had lower bone volume (63 vs 78 mm<sup>3</sup>,  $P=0.01$ ), bone volume/total volume (BV/TV) (19 vs 24 %,  $P=0.02$ ), bone mineral density (BMD) (169 vs 230 mgHA/cm<sup>3</sup>,  $P=0.04$ ), and bone mineral content (51 vs 74 mgHA,  $P=0.03$ ). For the day 10 onset regimen, torsional stiffness negatively correlated with callus BV/TV ( $r=-0.58$ ,  $P=0.03$ ) and callus BMD ( $r=-0.61$ ,  $P=0.02$ ).

**Conclusion:** This is the first study to demonstrate the positive effect of lithium administration on osteoporotic bone fracture healing. The proposed low-dose, 10-day onset treatment is a safe and translatable regimen providing guidelines for clinical evaluation of lithium toward enhancing fracture healing in osteoporotic patients.