**A Short Course of Dehydroepiadrosterone is Associated with Accelerated Fracture Healing in a Mouse Fracture Model**

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**Purpose:** Dehydroepiandrosterone (DHEA) is a metabolic intermediate in the biosynthesis of androgens and estrogens. DHEA supplementation in humans has been associated with increased bone mineral density and elevated systemic levels of insulin growth factor (IGF)-1, indicating that DHEA supplementation has the potential to improve fracture healing. The aim of this study is to assess the impact of a short course of DHEA on fracture healing in the setting of a translational fracture model. We hypothesize that DHEA will improve fracture healing and manifest this effect through osteoblast differentiation and matrix deposition.

**Methods:** A well-established murine fracture model generated middiaphyseal femur fractures in 10 young (12-week-old) and 10 aged (60-week-old) female C57BL/6 mice, stabilized with retrograde intramedullary pin placement. Half of the mice from each group were supplemented with 5 mg/kg/day DHEA. Micro-CT was performed at 2 weeks to assess callus morphology and mineral density. Histomorphometry of representative pentachrome-stained sections was performed to assess new bone formation. Skeletal stem and progenitor cells (SSPCs) were also harvested and grown in vitro in osteogenic culture medium to evaluate the effect of DHEA on osteoblasts.

**Results:** A total of 20 mice were available for analysis. Micro-CT demonstrates that DHEA significantly increases callus bone volume, bone volume/tissue volume (BV/TV), bone surface, and mineral density in aged mice, and significantly increases callus BV/TV, trabecular number, and mineral density in young mice. Histomorphometry demonstrates that DHEA significantly increases new bone formation in aged and young mice without affecting callus cartilage formation. Histologic evaluation revealed that mice treated with DHEA had a significant increase in the concentration of osteoblasts lining the fracture callus osteoid. In vitro studies demonstrated increased osteoblastogenesis in samples treated with DHEA in a dose-dependent manner, which is inhibited by androgen and estrogen receptor blockers.

**Conclusion:** Our study shows the positive effect of DHEA on the fracture healing process, likely through increased osteoblastogenesis via androgen and estrogen receptor signaling. DHEA is an oral supplement that may be beneficial for fracture repair.