

Post-traumatic bone loss following severe burn injuries in mice

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INTRODUCTION: Severe burn injuries lead to post-traumatic systemic bone loss, which could increase the risk of future fractures. This bone loss is driven by multiple mechanisms including early systemic hypercatabolism, proinflammatory cytokine release, disordered calcium metabolism, elevated stress hormones, and prolonged immobilization following burn injury. The relationship between bone loss and burn injuries is generally known, but has not been well characterized mechanistically because most of the previous studies are based on burn patients. Burn patients present with a wide range of burn area and severity, age, and health conditions, so there is a need for small animal models to investigate the mechanisms of post-burn bone loss and pharmacological treatments to prevent this bone loss. In this study, we used a burn model in mice to monitor the time course and magnitude of bone mineral density and bone microstructural changes after burn injury.

METHODS: Twenty 16-week-old male C57BL/6J mice were used for this study. Mice were randomly assigned to control or burn groups (n=10 per group). Three mice in the burn group were euthanized due to poor health conditions following injury. All mice were shaved on the dorsal side, anesthetized, then placed in a supine position in a mold with a 2x3 cm opening. To create the burn injury, the mold was immersed in 65°C water for 20 seconds, exposing only the 2x3 cm dorsal skin to the water. This procedure results in an approximately 20% surface area full thickness burn in 16 week-old male B6 mice. Burn debridement and surgical application of skin graft (Integra) was performed 48 hours after injury. Buprenorphine was administered twice a day for 48 hours for analgesia both after burn procedure and debridement, and sterile saline was injected subcutaneously to avoid dehydration. Sutures were removed after two weeks. All mice were single-housed throughout the experiment. Mice were anesthetized and imaged with dual-energy X-ray absorptiometry (Kubtec Parameter) at day -1 (prior to injury), 7, 14, 21, 28, 35, and 42 after the burn procedure to monitor bone mineral density (BMD) of the whole body, femoral diaphysis, and lumbar spine. All mice were euthanized 6 weeks after injury, and femora and lumbar spines were analyzed with micro-computed tomography (μ CT 35, SCANCO Medical AG) to measure trabecular and cortical bone microstructure.

RESULTS: Whole-body BMD in burn mice decreased following injury and reached a peak of -12% at week 3. In the lumbar spine, BMD decreased to a peak of -20% at week 2, while BMD in the femoral diaphysis decreased to -12% at week 2. All BMD measures recovered to control values by 6 weeks post-injury. μ CT analysis of the femur at week 6 showed significant decreases in trabecular bone volume fraction (BV/TV), trabecular number (Tb.N), apparent BMD, and connectivity density in the distal femoral metaphysis of mice that had burn injuries. At the femoral diaphysis, burn injuries led to significant decreases in cortical bone area (Ct.Ar) and total cross-sectional area (Tt.Ar).

DISCUSSION: This study characterized the time course and magnitude of the acute post-traumatic bone loss following severe burn in mice. Loss of BMD reached a peak at week 2-3 and then recovered to control values by 6 weeks. However, at 6 weeks post-injury we were still able to observe significant deficits in bone microstructure in mice with burn injuries. This time course is similar to what we have observed following femur fracture or myocardial infarction in mice, though the magnitude of bone loss observed in this study is considerably more severe. Our future studies will utilize this model to investigate specific mechanisms driving the post-traumatic bone loss response, and will investigate pharmacological treatments to prevent bone loss after burn, which may be able to decrease long-term bone deficits and decrease risk of fractures for patients who have suffered severe burn injuries.

SIGNIFICANCE/CLINICAL RELEVANCE: Post-traumatic systemic bone loss following severe burn may leave patients with permanent or long-term deficits in their bone health and increase their future fracture risk. Preventing this post-traumatic bone loss is therefore a critical goal for reducing secondary morbidity and mortality in burn patients. This study helps establish the time course and magnitude of systemic bone loss and recovery following severe burn in mice. Future studies will use this model to evaluate clinically relevant treatments for diminishing or preventing this bone loss.

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