INTRODUCTION: Diabetes mellitus remains one of the most common medical conditions affecting the adult population. Sustained hyperglycemia has been associated with a myriad of systemic pathological conditions, including peripheral neuropathy, kidney and gastrointestinal dysfunction, immunodeficiency, retinopathy, and tissue-repair disorders [1]. The impact of diabetes on the musculoskeletal system has only recently been explored. Studies have demonstrated a significant decrease in skeletal mass, bone mineral density, and impaired fracture healing in the diabetic population [1,2]. The purpose of this study was to determine the effect of a diabetic phenotype on tendon-bone healing after rotator cuff repair. We hypothesized that diabetic animals would demonstrate inferior histological and biomechanical characteristics at the healing enthesis compared to euglycemic controls.

MATERIALS & METHODS: Forty-eight male, Lewis rats underwent unilateral detachment of the supraspinatus tendon from the greater tuberosity followed by immediate anatomic repair with transosseous fixation. In the experimental group (n=24), diabetes was induced preoperatively via intraperitoneal injection of streptozocin (STZ, 65mg/kg) (Sigma, St. Louis MO), a selective toxin of pancreatic β-cells. Induction of diabetes was confirmed with both pre- and post-STZ injection intraperitoneal glucose tolerance tests (IPGTT) and only rats with a stable diabetic phenotype were included in the study. Control animals (n=24) received an intraperitoneal injection of citrate buffer solution only.

Twelve animals were sacrificed at 1 and 2 weeks postoperatively for biomechanical, histomorphometric, and immunohistochemical analysis. The tendon-bone interface was assessed with quantitative histomorphometry for metachromasia, collagen fiber orientation, as well as immunohistochemical staining for markers of neo-angiogenesis and advanced glycosylation end-products (AGE) (n=4/group). Stiffness and load-to-failure of the healing enthesis was tested at 1 and 2 weeks (n=8/group). Serum hemoglobin A1c (HbA1c) levels were measured at 2 weeks postoperatively to confirm the diabetic state. The severity of hyperglycemia as evaluated by area under the curve (AUC) IPGTT analysis was correlated with histologic and biomechanical outcomes (n=12/group). Statistical comparisons were performed using a student’s t-test with significance set at p<0.05.

RESULTS: Induction of Diabetes: STZ-induction of diabetes was both effective and sustained. Pre- and post-injection IPGTT demonstrated a significant impairment of glycemic control in the experimental group compared to control animals (p<0.05). Mean HbA1c level at 2 weeks postoperatively was 10.6±2.7% and 6.0±1.0% for the diabetic and control groups respectively (p<0.05). Mean AUC was significantly greater in the diabetic compared to control animals (20,000 versus 9,800 respectively) (p<0.05).

Histology: The healing enthesis of diabetic animals was atrophic and demonstrated a yellowish discoloration compared to the more robust, healthy tissue observed in control animals. Diabetic animals demonstrated significantly less fibrocartilage at the healing enthesis at 1 and 2 weeks postoperatively (p<0.05) (Figure 1). Evaluation of collagen birefringence revealed significantly less organized collagen in the diabetic group compared to control animals at both 1 and 2 weeks postoperatively (p<0.05) (Figure 2). Significantly greater advanced glycosylation endproducts (AGE) were noted in the supraspinatus tendon and enthesis of diabetic compared to control animals (p<0.05).

Biomechanical Testing: The healing enthesis of diabetic animals demonstrated a significantly reduced ultimate load-to-failure compared to control animals at both 1 and 2 weeks postoperatively (p<0.05) (Figure 3).

DISCUSSION: The metabolic state of poorly controlled diabetes impair tendon-bone healing after rotator cuff repair in this rodent model. Sustained hyperglycemia negatively influenced all histological and biomechanical parameters of healing at the enthesis. These findings have significant clinical implications for the expected outcomes of soft tissue repair or reconstructive procedures in diabetic patients with poor glycemic control. The fundamental mechanism of hyperglycemia-induced impairment of the tendon-bone healing response remains to be defined. Studies are in progress to define these mechanisms and assess the reversibility of impaired healing with tight preoperative and postoperative glycemic control. Local and systemic control of hyperglycemia may be more important than technical surgical factors on the outcome of rotator cuff repair in diabetic patients.