INTRODUCTION:
Tendinitis remains a catastrophic injury amongst athletes. Mesenchymal stem cells (MSCs) have been used empirically for the past several years in the treatment of tendinitis. To date, however, there are no studies documenting the efficacy of MSCs for tendinitis lesion repair. Additionally, previous work has demonstrated the value of growth factor injections, particularly insulin-like growth factor-I (IGF-I), to stimulate collagen deposition and tendon fiber deposition in the core lesion of tendinitis. While exogenous IGF-I has been shown to stimulate tendon healing in vivo, it has a short half-life and necessitates repeated dosing. The goal of this study was to examine the effects of MSCs as well as IGF-I gene-enhanced MSCs (AdIGF-MSCs) on tendon healing in vivo.

METHODS:
Sternal bone marrow aspirates were obtained from 12 normal young adult horses. MSCs were grown to confluency and stored frozen. Collagenase-induced lesions were created in the tensile region of the adult horses. Each horse served as its own control, with one forelimb randomly assigned as the treated limb and the other as the control. Five days post collagenase injection (t=0), 6 of the horses were treated with 10x10^6 MSCs and 6 horses were treated with 10x10^6 AdIGF-MSCs suspended in 1mL of PBS. AdIGF-MSCs were transduced with 500 MOI of AdIGF-I. Real-time PCR was used to confirm IGF-I gene expression. Control limbs were injected with 1mL of Earles. Horses were confined to stalls.

Ultrasound examinations of the tendons were performed at t=0, 2, 4, 6, and 8 weeks. Cross-sectional area (CSA) of the tendon and lesion, echogenicity, loss of linear fiber pattern, and compressibility were measured. Horses were euthanized at 8 weeks post treatment and entire SDFTs were harvested and mechanically tested to failure. Load data were normalized by CSA and stiffness was calculated from the slope of the CSA/strain curve. Following mechanical testing, entire tendon longitudinal segments through the lesion were collected. Longitudinal sections for histology were fixed in 4% PFA, embedded in paraffin, and analyzed using two-sample t-tests. Significance was set at p<0.05.

RESULTS:
Ultrasound data: There were no significant differences in ultrasound parameters within each group or between MSC and AdIGF-MSC treated tendons (data not shown).

Mechanical Testing: Only 1 of the 24 tendons failed at the lesion; 21 failed proximally and 2 failed distal to the lesion. Both MSC and AdIGF-MSC treated tendons were lower than control tendons, although this result was not significant (p=0.44) (Figure 1).

Histology: Cumulative scores were lower (improved) for treated compared to control tendons in both MSC and AdIGF-MSC groups. Perfect score=9; Worst score=36. Asterisk indicates a significant difference between treated and control tendons within each group (paired t-test, p<0.05).

DISCUSSION: These findings support the use of MSCs and IGF-I enhanced MSCs for the treatment of tendinitis. Histological scores were more normal for treated tendons compared to control tendons in both groups, and treated tendons in both groups had decreased stiffness compared to control tendons. In addition to the significant total histologic scores, there was a trend toward lower (more normal) histologic scores for nearly all parameters in AdIGF-MSC-treated tendons compared to MSC treated tendons, as well as a trend toward increased stiffness in AdIGF-MSC-treated tendons. Additional analyses including DNA, GAG, and total collagen content, immunohistochemistry for collagen types I and III, and catabolic gene expression patterns are warranted to further elucidate the differences in tendon healing between MSC and AdIGF-MSC treated tendons.