Introduction: The clinical outcomes of rotator cuff repair vary among patients and are affected by multiple factors including chronic inflammation. Although inflamed synovium is a common clinical observation at the time of surgery, the role of this inflammation plays on clinical outcomes is not well elucidated. Several recent studies have shown that there is elevation of pro-inflammatory cytokines (IL-1, IL-6, TNF-α, COX-2) and matrix metalloproteinases (MMP-1, MMP-13) in the synovium of torn tendon [1, 2, 3, 4, 5]. In addition, patients with increased IL-1β levels correlated with increased shoulder pain in rotator cuff diseases [6]. However, it is not clear from these studies whether such pro-inflammatory changes are affected by tear size (partial-thickness versus full thickness). The objective of this study was to test the hypothesis that tear size would affect pro-inflammatory cytokines, angiogenesis factors, and tissue remodeling genes in the synovium, bursa, and torn supraspinatus tendon present at the time of surgery.

Materials and Methods: Fourteen patients presented for arthroscopic rotator cuff repair (7 full, 7 partial) were prospectively enrolled. A small sample (~20 mm³) of synovium, bursa, torn supraspinatus tendon at the tear margin and the subscapularis tendon as a control in the operated shoulder were collected according to IRB-approved protocols. Samples were snapped-frozen in the operation room for mRNA isolation using a RNeasy mini kit (Qiagen) before reverse transcribed into cDNA (iScript, BioRad). Real time PCR was performed (BioRad) for selected pro-inflammatory factors (IL-1β, IL-6, TNF-α, COX2), angiogenesis factors (VEGF) and tissue-remodeling genes (MMP-1, MMP-9, TIMP-1, COL1A1, type III collagen, SMA and Biglycan). GAPDH was used as a housekeeping gene for reference. All the primers were designed and tested for real-time PCR based on a human cell-line stimulated by IL-1β. The identification and sequence of the samples were blinded and randomized according to HIPPA guidelines. Statistical analysis was performed using Excel (Microsoft) or Systat (10.2, SPSS) to determine the relationship between rotator cuff tear size and the level of pro-inflammatory cytokines, remodeling genes, and angiogenesis factors by the linear correlation and Student’s t-test. The significance level was set at 0.05.

Results: An increase of the IL-6 gene (p<0.05) in the synovium of the full-thickness group was found when compared to the partial thickness group. A similar trend of increase was also found in other pro-inflammatory cytokines including an increase in IL-1 and COX2 (Figure 1). Similar increase was also found in the tissue remodeling genes including TIMP-1 (p<0.05) and COL1A1 (p<0.05) in the full-thickness tears. However, in the bursa, no significant difference or trend was found in any gene except MMP-9 when comparing full thickness versus partial thickness tears (Figure 2). Our results also suggested rotator cuff tendon degeneration was closely related to pro-inflammatory and neovascularization factors. A strong correlation was found between angiogenesis genes (VEGF, MMP-9) and tendon-remodeling (type III collagen, Biglycan, p<0.001). There was also a close association between TIMP-1 and pro-inflammatory factors (IL-6, TNF-α, COX2, all p<0.01). An increase of VEGF (46.0±23.5-fold above the control) and type I collagen (20.7±4.3) genes were found in the full-thickness group as compared to the partial-thickness group.

Discussion: Our findings support our hypothesis that tear size can significantly affect pro-inflammatory genes (IL-6) as well as tissue remodeling (TIMP-1, MMP-1, and COL1A1) genes in the synovium from patients with rotator cuff tears in spite of a wide diversity of samples (gender, age, chronicity of tear, tear size of partial thickness.) Our findings also suggest that pro-inflammatory and neovascularization factors are closely associated with tendon remodeling and likely play a role in the pathogenesis of rotator cuff tears. This finding is consistent with previous studies [1, 2] that pro-inflammatory cytokines are closely related to angiogenesis and tissue remodeling in rotator cuff tendon. Further studies to determine the relationship between joint inflammation/tissue remodeling and clinical outcomes are warranted in order to elucidate the role inflammation has on the pathogenesis and repair of rotator cuff injury.


Acknowledgements: This study was supported in part by Institutes of Sports Medicine and a NIH grant (AR50549). The authors thank Drs. Edward Craig, Frank Cordasco, and Struan Coleman for their contribution.

Figure 1. Pro-inflammatory gene expression in synovium as normalized to GAPDH using real-time PCR. * indicated p<0.05 between partial-thickness and full-thickness groups.

Figure 2. Pro-inflammatory gene expression in bursa as normalized to GAPDH using real-time PCR.