

Proinflammatory Cytokines are Expressed in the Greater Tuberosity after Rotator Cuff Tears

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INTRODUCTION:

Pain after rotator cuff tears is not well understood. Previous studies have demonstrated the role of subacromial bursa, rotator cuff tendon, and synovium in pain generation. However, no prior study has investigated the role of the greater tuberosity (GT). Our goal was to compare proinflammatory cytokine expression in the GT in painful patients undergoing arthroscopic rotator cuff repair (RCR) versus painless patients undergoing shoulder stabilization as a control.

METHODS: This was a prospective cohort study of patients undergoing arthroscopic RCR or anterior shoulder stabilization surgery between 2022-2023 at a single institution (IRB 2022-14603). Patients were excluded if they had open physes, fractures, frozen shoulder, rheumatoid arthritis, or prior shoulder surgery (Figure 1). Demographic variables included: age, sex, pain (graded as “no pain,” “mild pain,” “moderate pain,” or “severe pain”), and duration of symptoms. An arthroscopic curette of ~2 mm depth was used to collect subchondral bone at the exposed GT at the region of the full thickness cuff tear, or bony region of suture anchor placement prior to remplissage. Samples were immediately stored in 500 ul of RNeasy lysis solution at 4 C following surgery, then transferred to a -80 C at the end of the surgical day. RNA was extracted using a kit, and quantitative polymerase chain reaction (qPCR) was used to compare mRNA expression levels of cytokines: nerve growth factor (NGF), monocyte chemoattractant protein-1 (MCP1), tumor necrosis factor alpha (TNF- α), interleukin-6 (IL-6), IL-1 β , and matrix metalloproteinase (MMP-1). Data were compared using student t-test and chi-square test.

RESULTS:

Fifteen total patients (11 rotator cuff, 4 shoulder instability) were enrolled after inclusion/exclusion criteria (Table 1). All patients with rotator cuff tears described their pain as “moderate,” whereas those with shoulder instability either had “no pain” (2/4) or “mild pain” (2/4) (Table 1). All patient RNA quality was deemed pure for nearly all samples. This was defined by a 260/280 ratio of 1.8-2.1 following RNA isolation (Table 2). When compared to shoulder instability patients, rotator cuff deficient patients demonstrated statistically increased levels of various proinflammatory cytokines including: NGF (1.7x), MCP-1 (2.8x), TNF α (4.5x), and IL-6 (5x) from the GT. Levels of IL-1 β and MMP-1 were statistically similar between cohorts (Figure 2).

DISCUSSION AND CONCLUSION:

Pain after rotator cuff tears is multifactorial. An exposed GT may be a significant source of proinflammatory cytokines in rotator cuff deficient patients. To the authors’ knowledge, this is the first study in humans that describes the isolation and analysis of proinflammatory cytokines from the GT. Similar to prior studies in knee osteoarthritis models, levels of TNF α and IL-6 were elevated in rotator cuff deficient patients. Limitations to this study include a limited patient size and confounding factors innate to the retrospective cohort design, such as: chronicity of injury, patient comorbidities, and age. However, this study may set a foundation for future basic science studies of rotator cuff repair. For example, the proinflammatory cytokine profile of patients with rotator cuff arthropathy should be analyzed. Additionally, examining how coverage of the GT may affect the proinflammatory cytokine profile in the shoulder may improve understanding of rotator cuff repair.

Figure 1. Flowchart of Patient Recruitment



Figure 2. Analysis of Proinflammatory Cytokine Expression

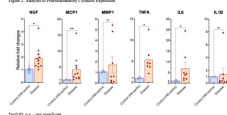


Table 1. Demographic Data

	Rotator Cuff Deficiency (n=11)	Shoulder Instability (n=4)
Age (yr)	48.2 (5.5)	29.8 (7.3)
Sex (M/F)	5/6	3/1
Duration of Symptoms (mo)	18.2 (10.4)	48.8 (23.8)
Preoperative Pain	Moderate (11/11)	No Pain (2/4), Mild (2/4)
Impingement Sign on Exam	Yes (11/11)	No (4/4)
Strength Normal on Exam	Yes (11/11)	Yes (4/4)
Strength/Endeavor Retained	4/3 (11/11)	3/1 (4/4)

Table 2. Quality Control of RNA Samples

Patient #	Sample ID	Nucleic Acid	A ₂₆₀ /A ₂₈₀	A ₂₆₀ /A ₃₂₀	260/280	Sample Type
1	C1	ng/ml	1.788	0.911	1.82	RCT
2	C2	ng/ml	1.820	0.91	1.94	RCT
3	R1	ng/ml	1.869	0.947	1.97	RCT
4	R2	ng/ml	1.680	0.999	1.67	RCT
5	R3	ng/ml	1.412	0.722	1.97	RCT
6	R4	ng/ml	1.280	1.088	1.98	RCT
7	R5	ng/ml	1.618	0.861	1.88	RCT
8	R6	ng/ml	1.586	0.902	1.68	RCT
9	R7	ng/ml	2.026	2.491	2.02	RCT
10	C3	ng/ml	0.917	0.770	1.19	RCT
11	C4	ng/ml	0.736	0.419	1.76	RCT
12	C5	ng/ml	1.887	1.048	1.86	RCT
13	C6	ng/ml	1.048	0.829	1.26	RCT
14	C7	ng/ml	1.181	1.119	1.04	RCT
15	R8	ng/ml	0.927	0.562	1.63	RCT