Tissue Inhibitor of Metalloproteinase as a Synovial Fluid Biomarker of Post-Operative Pain Following Anterior Cruciate Ligament Reconstruction

Andrew J Clair MD, Utkarsh Anil BA, Matthew T Kingery BA, Lena Kenny MSc, Eric J Strauss MD

NYU Langone Health
Department of Orthopaedic Surgery, Division of Sports Medicine

INTRODUCTION

Following ACL reconstruction, patients must undergo rehabilitation to achieve adequate mobility, strength, and knee range of motion before returning to an active lifestyle

Obtaining a better understanding of the underlying processes and risk factors associated with pain following ACL reconstruction may lead to the development of more individualized analgesic and rehabilitation programs

With a better understanding of the intra-articular microenvironment following ACL injuries, the orthopaedic surgeon may be able to better manage their patients with individualized post-surgical expectations and rehabilitation timelines

PURPOSE

To investigate the association between synovial fluid biomarkers found in ACL-injured knees at the time of surgery and early postoperative clinical outcomes including pain, range of motion, and symptomatic joint effusion

METHODS

- This was a single-center IRB-approved study in which patients were prospectively enrolled between February 2012 and October 2017
- Synovial fluid samples were collected in the operating room after sterile preparation prior to the surgical incision
- The samples were transferred to sterile tubes containing a protease inhibitor cocktail solution (Halt Protease Inhibitor Cocktail, EDTA-free; Pierce Biotechnology, Rockford, IL)
- Samples were centrifuged at 3820 rpm for 10 minutes, and the supernatant was aliquoted into sterile tubes before storage at -80º C
- The concentrations of 10 synovial fluid biomarkers of interest were determined using custom and standard pre-coated multiplex Human V-PLEX Plus ELISA plates (Meso Scale Discovery, Rockville, Maryland, USA)
- Patient-reported pain level on a visual analog scale was recorded at the first postoperative visit
- Patients were categorized as high pain (VAS ≥ 5) or low pain (VAS < 5) based on their reported VAS pain score

RESULTS

- The current study included synovial fluid samples from 105 patients (mean age 32.17 +/- 9.03 years) undergoing surgery for primary ACL reconstruction with bone-tendon-bone (BTB) autograft
- There was a statistically significant positive correlation between synovial fluid concentration of TIMP-2 and early postoperative VAS ($r = 0.271$, $p = 0.005$)
- When comparing the high pain and low pain group, there was a statistically significant difference in the synovial fluid concentration of TIMP-1 (258,848.30 pg/mL vs 180,848.10 pg/mL, $p = 0.04$) and TIMP-2 (84,490.86 pg/mL vs 50,546.60 pg/mL, $p = 0.02$)
- There were no statistically significant relationships between synovial fluid biomarker concentrations and incidence of symptomatic joint effusions or deficits in post-operative range of motion

The mean concentration (pg/mL) of synovial fluid biomarkers in the high pain group (VAS ≥ 5) and low pain group (VAS < 5).

Biomarker	High Pain	Low Pain	P Value
RANTES	951.16	1,093.12	0.8047
IL-6	157.65	73.23	0.9185
MCP-1β	323.25	401.80	0.5065
MIPB	45.41	51.35	1.0000
MMP-3	2,951,286.89	2,590,120.10	0.3983
TIMP-1	258,848.30	180,848.10	**0.0389**
TIMP-2	84,490.86	50,546.60	**0.0189**
IL-1Ra	135.00	216.40	0.5064
VEGF	300.55	278.22	0.6024
bFGF	80.33	34.55	0.5319

DISCUSSION

In a study evaluating 10 different pro- and anti-inflammatory synovial fluid biomarkers following ACL injury collected at the time of surgery, two anti-inflammatory cytokines (TIMP-1 and TIMP-2) were found to be significantly elevated in patients reporting higher pain levels (VAS ≥ 5) compared with those reporting lower pain levels (VAS < 5) in the early post-operative period

Elevations in TIMP-1 and TIMP-2 are consistent with reports in the literature showing similar findings in synovial fluid concentration of knees following ACL tears

Both TIMP biomarkers are anabolic cytokines with anti-inflammatory properties

While MMP-3 is a known enzyme important in cartilage degradation and remodeling, the TIMP family of cytokines inhibit this and other metalloproteinase action

Upregulation of MMP expression in chondrocytes has been documented following articular injury

In addition, it is also believed that in the presence of abnormal joint loading, such as that seen in the knee post ACL injury, there is increased activity of MMP

The fact that there is a well documented increase in MMP activity within the intra-articular environment following an ACL injury, it stands to reason that the natural response is a simultaneous increase in TIMP expression

SIGNIFICANCE

Patients reporting higher levels of pain in the acute postoperative period after ACL reconstruction have significantly elevated levels of TIMP-1 and TIMP-2 in their synovial fluid at the time of surgery

With the widespread overuse and misuse of opioids for the management of postoperative pain, there is increased attention directed towards curbing excessive narcotic prescriptions

Based on this data, Tissue Inhibitor of Metalloproteinase may be a predictive synovial biomarker for pain, capable of clinical use in formulating individualized post-operative analgesic and rehabilitation regimens following ACL reconstruction