Role of Synovial Fluid Cytokines in Assessing Long-Term Outcomes following Anterior Cruciate Ligament Reconstruction

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INTRODUCTION: Anterior cruciate ligament (ACL) injury is a common orthopaedic injury that often results in long-term complications, such as posttraumatic osteoarthritis (PTOA). Synovial fluid biomarkers have emerged as a potential tool for understanding the pathophysiology of degenerative joint disease and predicting long-term patient outcomes following ACL injury. This study aimed to investigate the correlation between long-term patient-reported outcomes and synovial fluid biomarker concentrations.

METHODS:

Starting January 2011, patients undergoing knee surgery were prospectively recruited for inclusion in an ongoing synovial fluid database. Synovial fluid was collected preoperatively from these patients from the knee undergoing surgery and the concentrations of 10 cytokines were measured. From this cohort, 26 patients who underwent an ACL reconstruction (ACLR) and had cytokine results were surveyed for patient-reported outcomes (PROs) including Pain Visual Analog Scale (VAS), the Knee Disability and Osteoarthritis Outcome Score Physical Function Shortform (KOOS-PS), and Lysholm scores at a minimum of 10 years follow up. Principal component analysis and hierarchical clustering were employed on the cytokine data to create a predictive linear regression model for patient-reported outcomes and identify unique patient clusters characterized by comparable synovial fluid profiles. PROs and log-transformed cytokine concentrations were compared between the clusters using t-test.

RESULTS: Of the 26 patients with 10 year PROs, 3 underwent additional procedures in the same knee and were subsequently excluded from analysis. The final cohort was composed of 23 patients with a mean age at surgery of 34.96 ± 10.42 years, current age of 45.87 ± 10.77, Body Mass Index (BMI) of 25.41 ± 4.80, and an average follow-up time of 10.91 ± 0.61 years. The first two principal components explained 61.90% of the cytokine data variance. A regression model with PC1 and PC2 explained 49.95% of the variance in long-term Lysholm scores and 40.10% variance in VAS pain scores. Hierarchical clustering on PC1 and PC2 was used to create three patient clusters, two of which contained the majority of the cohort. Cluster 1 (n=9) had significantly higher Lysholm scores compared to Cluster 2 (n=13) (92.67 vs. 82.31, p=0.007), lower log-transformed concentrations of IL-6 (0.70 vs. 4.92, p < 0.001), MCP-1 (5.70 vs. 6.18, p = 0.011), VEGF (5.18 vs. 6.34, p = 0.001), and MMP-3, (14.14 vs. 15.85, p = 0.008), and higher concentrations of bFGF (4.02 vs. 2.06, p = 0.008). There were no differences in age, sex, or BMI between the clusters.

DISCUSSION AND CONCLUSION: The analysis of specific concentrations of cytokines present in synovial fluid, including IL-6, MIP-B, VEGF, MMP-3, and bFGF, offers valuable insights into the intra-articular microenvironment subsequent to knee injury. This study identified a distinct patient cluster characterized by lower levels of pro-inflammatory cytokines (IL-6, MIP-1B, MMP-3) and higher levels of growth factor biomolecules (bFGF) at the time of surgery. Assessing these biomarkers at the time of ACLR may help anticipate long-term functional outcomes and pain levels at 10 years postoperatively. This can guide clinicians in developing targeted interventions such as administration of anti-inflammatory biologics other approaches to modulate the inflammatory response.

	Cluster 2	Cluster 3	p value
Follow Up Time (years)	10.68 (0.67)	11.04 (0.55)	0.192
Log Transformed Biomarker Concentration			
RANTES	4.09 (1.39)	4.61 (1.80)	0.469
Il-6	0.70 (0.96)	4.92 (1.63)	**<0.001**
MCP-1	5.70 (0.43)	6.18 (0.36)	**0.011**
MIP-B	3.36 (0.66)	3.90 (1.03)	0.18
VEGF	5.18 (0.93)	6.34 (0.48)	**0.001**
TIMP-1	12.95 (0.35)	12.95 (0.11)	0.943
TIMP-2	11.19 (0.74)	11.01 (0.59)	0.549
IL-1Ra	4.94 (0.72)	5.94 (1.41)	0.065
MMP-3	14.14 (1.73)	15.85 (0.85)	**0.006**
BFGF	4.02 (1.90)	2.06 (1.26)	**0.008**
Patient Reported Outcomes			
VAS Pain	6.56 (9.72)	11.92 (19.50)	0.457
Lysholm	92.67 (6.08)	82.31 (9.10)	**0.007**
KOOS-PS	93.19 (6.34)	86.34 (11.80)	0.129
Tegner Prior to Injury	7.33 (1.66)	6.31 (2.29)	0.264
Tegner Current	5.78 (1.20)	5.31 (2.32)	0.585