Characterization of Synovial Fluid Inflammatory Biomarkers at the Time of Anterior Cruciate Ligament Reconstruction and Changes on Preoperative MRI

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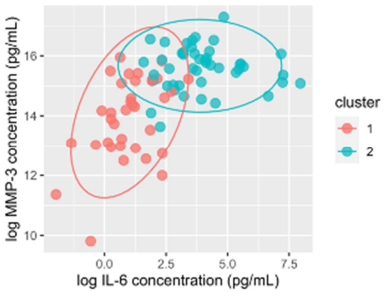
INTRODUCTION: Despite improvements in anterior cruciate ligament reconstruction (ACLR) techniques, ACL injuries continue to be a significant risk factor for early-onset post-traumatic osteoarthritis (PTOA). Although poorly understood, contributing factors may include tissue insult from the initial ACL injury and secondary insult from the ACLR surgery resulting in the release of pro-inflammatory cytokines into the intra-articular environment. In addition to tearing the ACL, there are often concomitant osseous and chondral injuries not visible on plain radiography at the time of initial ACL injury, which also may contribute to the inflammatory cascade leading to PTOA. This study explores the relationship between these pathological MRI findings and inflammatory biomarkers at the time of surgery. We hypothesize that higher synovial fluid concentrations of pro-inflammatory biomarkers will be strongly associated with more severe knee joint morphological features on MRI as indicated by the ACL osteoarthritis sore (ACLOAS) and its component subscores.

METHODS: Patients undergoing surgery for ACL injury from October 2011 to December 2021 were included in a database of subjects who had synovial fluid samples collected at the time of surgery. From this cohort, 82 subjects with acute ACL injury were retrospectively selected who met the following inclusion criteria: no history of prior knee trauma to suggest chronic ACL injury, history of an acute non-contact knee injury, MRI examination of the knee performed within three weeks of knee injury, subsequent knee surgery performed between 4 and 12 weeks of knee injury, and no other ligament tear. All subjects underwent a preoperative MRI examination of the knee using multi-planar, multi-contrast fast spin-echo sequences. Synovial fluid was aspirated from the operative knee prior to surgical incision. Concentrations of inflammatory biomarkers, including regulation on activation of normal T cell expressed and secreted (RANTES), interleukin 6 (IL-6), vascular endothelial growth factor (VEGF), tissue inhibitor matrix metalloproteinase-1 (TIMP1), interleukin 1 receptor agonist (IL1-RA), and matrix metalloproteinase 3 (MMP-3) were measured. A fellowship-trained musculoskeletal radiologist reviewed the MRI examinations of all subjects to assess the presence and severity of various MRI features of acute and chronic knee injury using the validated ACLOAS system. K-means cluster analysis controlling for age and time from injury to surgery was used to identify 2 distinct clusters of subjects based on synovial fluid biomarker concentrations. Nonparametric Mann Whitney-U tests and Fisher's exact tests were used to compare demographic factors, MRI findings, clinical symptoms, and synovial fluid inflammatory biomarkers between clusters.

RESULTS: The mean age of the cohort was 31.6 ± 8 years, average body mass index (BMI) was 25.5 ± 4.4 kg/m2. In total, 42.7% (n=35) of the cohort was female and 85.4% (n=70) were non-smokers. Two distinct clusters were identified: Cluster 2 was characterized by significantly greater concentrations of all inflammatory cytokines (Table 1). When controlling for age and the duration from injury to the time of aspiration, Cluster 2 again demonstrated significantly greater concentrations of all inflammatory cytokines. Furthermore, when controlling for age and duration of injury, Cluster 2 was characterized by significantly worse function as assessed by Lysholm score ($p < 0.001$). Also, when controlling for age and duration of injury, Cluster 2 was characterized by a greater ACLOAS effusion score ($p = 0.042$), greater Hoffa synovitis score ($p = 0.024$), and greater odds of an associated osteochondral fracture ($p = 0.004$) on MRI.

DISCUSSION AND CONCLUSION: This study revealed that there might be a distinct pro-inflammatory intraarticular phenotype following an ACL injury that is characterized by higher concentrations of biomarkers, effusion, and synovitis. These results provide insight into the complex pathophysiology underlying ACL injury and could help guide future management toward more personalized interventions based on these biochemical and imaging parameters.



Cytokine	Cluster 1	Cluster 2	P value
RANTES	4.072255	5.274814	**0.006**
IL-6	1.000331	3.978454	**< 0.001**
VEGF	5.126516	6.033147	**< 0.001**
TIMP-1	11.49364	12.73725	**0.002**
IL-1Ra	4.452285	5.614808	**< 0.001**
MMP-3	13.94701	15.59388	**< 0.001**

Table 1. All cytokine concentrations are log transformed.