Chemokine C-C Motif Ligand-5 and Basic Fibroblast Growth Factor Concentration at the Time of Surgery Can Predict Postoperative Stiffness in Patients Undergoing ACLR

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INTRODUCTION:
Patients undergoing anterior cruciate ligament reconstruction have been shown to be at risk for postoperative arthrofibrosis. Diagnostic biomarkers associated with development of stiffness are unknown. We hypothesize that biomarkers found in the synovial fluid at the time of surgery are associated with development of postoperative arthrofibrosis in a cohort of patients undergoing anterior cruciate ligament reconstruction.
METHODS: Patients undergoing anterior cruciate ligament reconstruction were prospectively enrolled. Synovial fluid was collected in the OR prior to surgical incision. A cohort of patients with postoperative stiffness requiring manipulation under anesthesia or lysis of adhesions was identified. Matching of case to controls was performed using a 1:2 pair matching algorithm. Clinical factor-adjusted single biomarker and multivariable models were used to assess the association of biomarkers with postoperative stiffness requiring manipulation under anesthesia (MUA) or lysis of adhesions (LOA).

RESULTS: A total of 11 (n = 3 male, n = 8 female) patients undergoing ACLR met inclusion criteria, matched with 21 (n = 6 male, n = 15 female) controls with no significant differences in age, sex, smoking history, or days from injury to surgery. Levels of CCL5/RANTES were significantly higher in cases versus controls (694.20 [214.75 - 3428.79] vs. 113.04 [32.81 - 517.91]; p=0.034). Interleukin-1 Receptor Antagonist (IL-IRA), bFGF, and RANTES were found to have greatest predictive value by the final stepwise logistic regression model. Independent predictors of increased risk of postoperative stiffness after ACLR included RANTES (OR [95% CI]) (2.28 [1.29 – 5.37]; p=0.019) and bFGF (1.91 [1.07 – 3.99]; p=0.047) according to a multivariable logistic regression model. Only RANTES was a statistically significant predictor of developing postoperative stiffness (OR [95% CI]) (2.59 [1.26-9.07]; p=0.046).
DISCUSSION AND CONCLUSION: This study identifies two biomarkers that can predict the risk of developing arthrofibrosis after ACL reconstruction. Elevated levels of bFGF and RANTES/CCL5 were found in the synovial fluid of patients who experienced clinically significant postoperative stiffness requiring manipulation under anesthesia or lysis of adhesions. This finding highlights the role of biology and inflammatory response in the development of this condition and further investigations of potential treatments aimed to interrupt the fibrotic pathway and prevent arthrofibrosis.

Table 1. Demographic and Clinical Characteristics of Cohort

Variable	*Cases (n = 11)*	*Control (n = 21)*	*P-value*
Age (y), mean ± SD	31.13 ± 6.62	31.02 ± 7.11	0.967[a]
Sex, n (%)			0.938[b]
Female	8 (72.7%)	15 (71.4%)	
Male	3 (27.3%)	6 (28.6%)	
BMI, mean ± SD	24.3 ± 3.9	24.8 ± 3.13	0.699[a]
Smoking Exposure			0.773[b]
Never Smoker	9 (81.8%)	18 (85.7%)	
Ever Smoker	2 (18.2%)	3 (14.3%)	
Injury, n (%)			0.907[b]
ACL	5 (45.4%)	10 (47.6%)	
ACL + Meniscus	6 (54.5%)	11 (52.4%)	
Concomitant Procedures, n (%)			
Meniscal Repair	6 (54.5%)	8 (38.1%)	0.938[b]
Meniscectomy	3 (27.3%)	5 (23.8%)	0.830[b]
Graft Choice			0.654[b]
BPTB Autograft	8 (72.7%)	16 (76.2%)	
BPTB Allograft	2 (18.2%)	1 (4.8%)	
Tibialis Anterior	1 (9.1%)	2 (9.5%)	
Hamstring Allograft	0 (0%)	2 (9.5%)	
Days from Injury to Surgery, mean ± SD	51.55 ± 21.14	45.38 ± 16.56	0.371

a. t-test
b. Chi-Squared test
* The significance level is 0.05

Table 2. Summary of Interventions for Cases

	Median (IQR)
Time to MUA/LOA (days)	92 (69 – 98)
Loss of Flexion (degrees)	35 (10 – 65)
Loss of Extension (degrees)	2 (0 – 5)

MUA, manipulation under anesthesia; LOA, lysis of adhesions

Table 3. Biomarker Concentration in study population

	Cases	Controls	
Biomarkers	*Median (IQR)*	*Median (IQR)*	*P-value*
RANTES (pg/ml)	694.20 (214.75 - 3428.79)	113.04 (32.81 - 517.91)	**0.034**[c]
IL-6 (pg/ml)	12.750 (1.89 - 31.2)	24.6 (3.5 - 41.96)	0.506
VEGF (pg/ml)	244.917 (132.39 - 339.96)	364.67 0(253.88 - 548.82)	0.238
TIMP1 (ng/ml)	364.06 (18.76- 1371.97)	345.07 (23.05 – 700.38)	0.907
IL-1RA (pg/ml)	162.30 (65.080 - 464.17)	144.11 (84.13 - 283.93)	0.938
MMP3 (ng/ml)	3304.95 (517.61- 8428.38)	5397.54 (2093.24- 9223.37)	0.785
MCP-1 (pg/ml)	381.04 (193.9 - 447.15)	436.01 (287.9 - 490.39)	0.194
MIPB (pg/ml)	34.15 (20.17 - 50.05)	45.5 (30.07 - 56.22)	0.250
BFGF (pg/ml)	54.14 (3.3 - 121.88)	6.51 (3.29 - 15.43)	0.133

a. RANTES/CCL5, Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted/Chemokine C-C motif Ligand 5; IL-6, interleukin-6; IL-1RA, Interleukin-1 Receptor Antagonist; VEGF, Vascular Endothelial Growth Factor; MMP-3, Matrix Metalloproteinase-3; TIMP-1, Tissue Inhibitor of Metalloproteinases-1; MIPB, Macrophage Inflammatory Protein; MCP, Monocyte Chemotactic Protein; BFGF, Basic Fibroblast Growth Factor.
b. Significance level set at 0.05
c. Mann-Whitney U Test