RELATIONSHIP OF SYNOVIAL FLUID CYTOKINES AND MIDTERM PATIENT REPORTED OUTCOMES FOLLOWING ARTHROSCOPIC PARTIAL MENISCECTOMY

Amanda Avila MPH, Dhruv S. Shankar, Matthew T. Kingery, Kinjal Vasavada, Samuel R Montgomery, Calvin T. Chang, Eric J Strauss MD

[1]Division of Sports Medicine, NYU Langone Health, New York, NY

NYU Langone Health

NYU Langone Orthopedics

Disclosures

- Eric Strauss:

  AAOS: Board or committee member, American Orthopaedic Association: Board or committee member, Arthrex, Inc: Paid consultant; Paid presenter or speaker, Arthroscopy Association of North America: Board or committee member, Better PT: Stock or stock Options, Cartiheal: Research support, Cartilage, Bulletin of the Hospital, For Joint Diseases: Editorial or governing board, Fidia: Research support, Flexion Therapeutics: Paid consultant, Jaypee Publishing: Publishing royalties, financial or material support, Joint Restoration Foundation: Paid consultant, Organogenesis: Paid consultant; Paid presenter or speaker; Research support, Smith & Nephew: Paid consultant; Paid presenter or speaker, Springer: Publishing royalties, financial or material support, Subchondral Solutions: Paid consultant, Vericel: Paid consultant; Paid presenter or speaker

NYU Langone
Orthopedics

NYU Langone
Health

Background

- Arthroscopic partial meniscectomy (APM) is one of the most commonly performed surgical procedures for meniscus tears

- However, the relationship between meniscal injury and the progression to osteoarthritis is poorly understood

- Given the variable outcomes following APM, synovial fluid (SF) biomarkers may hold promise as indicators of patients for whom APM may be beneficial

NYU Langone
Orthopedics

NYU Langone
Health

Purpose

- The purpose of this study was to explore the association between preoperative synovial fluid biomarkers and postoperative patient reported outcomes following APM.

NYU Langone
Orthopedics

NYU Langone
Health

Methods

- Patients who underwent APM from October 2011 to December 2020 were included in a database of subjects who provided SF samples at the time of surgery and completed preoperative questionaries

- Concentrations of synovial fluid (SF) biomarkers were measured using ELISA

- At a minimum of 2 years of follow-up, patient-reported outcomes were collected including Lysholm, Tegner activity score, and a visual analog scale (VAS) for pain

NYU Langone
Orthopedics

NYU Langone
Health

Methods

- Patients were grouped into those who improved defined as those who met the Lysholm minimal clinically significant difference (MCID), +12.3 points

- Change in outcome scores were compared using paired t-test and non-parametric tests.

- Generalized linear models adjusted for age, sex, BMI, smoking status, time to follow up, time from injury to surgery, and K-L grade used to identify which biomarkers were associated with improvement in Lysholm, VAS pain, and KOOS Physical Activity score.

**NYU Langone
Health**

Methods

Table 1. Summary of the Basic Functions of Included Biomarkers		
Type of Biomarker	Biomolecule	Basic Function
Cytokines	IL-6	Cytokine secreted by T cells and macrophages during infection or after trauma; stimulates IL-10 and IL-1RA production to act in a negative feedback loop of inflammatory response
	IL-1RA	Cytokine that inhibits the pro-inflammatory effect of IL-1B
Chemokines	MIP-B	Chemokine produced by neutrophils; activates granulocytes and recruits neutrophils, monocytes, macrophages, immature dendritic cells, and Th1 cells to the site of inflammation.
	MCP-1	Chemokine that recruits monocytes, memory T-cells and dendritic cells to the site of inflammation.
	RANTES/CCL5	Chemokine that recruits leukocytes to the site of inflammation and activates natural killer cells
Growth factors	VEGF	Growth factor that induces angiogenesis
	BFGF	Promotes chondrogenesis, angiogenesis, wound healing, granulation tissue formation
Catabolic factors	MMP-3	Metalloproteinase that degrades collagen II, IV, IX, X, XI, proteoglycans, fibronectin, laminin, and elastin; can activate other MMPs.
	TIMP-1	A class of proteins that inhibits MMPs; promotes cell growth of chondrocytes and has chondroprotective effect

NYU Langone Orthopedics

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

NYU Langone Health

Results

- A total of 50 patients were included in this study, of those 34 patients (68%) met Lysholm MCID and 16 did not

- The mean age of the cohort is was 51 ± 9 years (p=0.35), both groups were majority male (p=0.37).

- Follow-up time was not significantly different between groups (MCID 64.9 months vs non-MCID 72.6 months, p=0.20)

- MMP-3 levels at the time of surgery were significantly higher among those who did not meet MCID, 2337.57 ± 3965.58 ng/m (p = 0.03).

- Among those who did not achieve Lysholm MCID, change in VAS pain (p=0.706) and Tegner activity level (p=0.756) were not found to be significant

Results: Cohort demographics and clinical information

	Full Cohort	Met MCID	Did Not Meet MCID	p-value
	(n = 50)	(n = 34)	(n = 16)	
Age (y)	51.0 ± 9.0	52.1 ± 9.9	49.4 ± 7.6	0.35[a]
BMI (kg/m²)	29.6 ± 4.8	29.4 ± 5.3	29.6 ± 4.9	0.74[a]
Time from injury to surgery (w)	44.9 ± 50	43.9 ± 56.5	47.1 ± 44.7	0.53[b]
Follow-up time (m)	67.38 ± 19.4	64.9 ± 17.4	72.6 ± 23.0	0.20[a]
Sex				
Female	21 (42.0%)	16 (47.1%)	5 (31.3%)	0.37[c]
Male	29 (58.0%)	18 (52.9%)	11 (68.8%)	
Smoking Status				
Current Smoker	4 (8.0%)	2 (5.9%)	2 (12.5%)	0.17[c]
Former Smoker	12 (24.0%)	6 (17.6%)	6 (37.5%)	
Never Smoker	34 (68.0%)	26 (76.5%)	8 (50.0%)	
Mechanism of Injury				
Degenerative	26 (52.0%)	16 (47.1%)	10 (62.5%)	0.37[c]
Trauma	24 (48.0%)	18 (52.9%)	6 (37.5%)	
KL-Grade				
0 or 1	40 (80.0%)	29 (85.3%)	11 (68.8%)	0.26[c]
2 or 3	10 (20.0%)	5 (14.7%)	5 (31.3%)	
Failed Non-Operative Treatment Prior to Meniscectomy	41 (82.0%)	28 (82.4%)	13 (81.3%)	0.93[c]
Concomitant Chondroplasty	29 (58.0%)	18 (52.9%)	11 (68.8%)	0.37[c]

Results: Pre-to-postoperative improvement in VAS pain and Lysholm Scores

Outcome	Improvement in VAS Pain		Improvement in Lysholm		Postoperative KOOS-PS	
	Score		Score		Score	
Predictor	Estimate	p	Estimate	p	Estimate	p
(Intercept)	148.45	0.05	82.86	0.2	80.81	0.13
Time From Injury to Surgery (w)	0.03	0.7	0	0.98	0.05	0.42
Age (y)	-0.05	0.92	0.26	0.54	0.24	0.49
Sex: Male	-15.06	0.11	-2.21	0.78	11.27	0.08
BMI	-1.24	0.18	-0.47	0.55	-0.8	0.22
KL Grade (Mild vs Moderate/Severe)	2.12	0.85	-5.73	0.54	-0.85	0.91
Ever Smoker	-3.56	0.69	-12.9	0.09	-9.98	0.11
Time to Follow Up (m)	0.46	0.040[a]	-0.16	0.38	-0.29	0.06
RANTES (pg/mL)	-6.3	0.040[a]	-3.61	0.18	-0.13	0.95
IL-6 (pg/mL)	1.4	0.62	-0.41	0.87	-0.68	0.73
VEGF (pg/mL)	12.93	0.08	9.75	0.12	0.34	0.95
IL-1 RA (pg/mL)	7.89	0.27	12.57	0.04[a]	9.43	0.06
MMP-3 (pg/mL)	-15.16	0.001[a]	-10.34	0.007[a]	-1.24	0.69
R^2	0.41		0.37		0.34	

NYU Langone Health

Conclusion

- This study found that elevated intraarticular levels of MMP-3 and RANTES at the time of surgery are associated with poor midterm outcomes and persistent pain following APM. Additionally, higher levels of IL-1Ra at the time of surgery were associated with greater improvement in midterm postoperative outcomes

- These results suggest that in addition to serving as indicators of postoperative prognosis, these candidate synovial fluid biomarkers may be targets for treatment to improve outcomes following the arthroscopic treatment of symptomatic meniscus tears

NYU Langone
Health

References

1. Kingery, Matthew T., et al. "Synovial fluid cytokine profile at the time of arthroscopy explains intermediate-term functional outcomes." *The American Journal of Sports Medicine* 50.5 (2022): 1261-1271.
2. Avila, Amanda, et al. "RANTES Concentration at the Time of Surgery Is Associated With Postoperative Stiffness in Patients Undergoing ACL Reconstruction." *The American Journal of Sports Medicine* 50.14 (2022): 3838-3843.
3. Montgomery SR, Zhang A, Ngo SS, Wang JC, Hame SL. Cross-sectional analysis of trends in meniscectomy and meniscus repair. *Orthopedics*. 2013;36(8):e1007-1013.
4. Krych AJ, Stuart MJ, Levy BA. Arthroscopic Partial Meniscectomy for Degenerative Meniscal Tear. *New England Journal of Medicine*. 2014;370(13):1259-1261.
5. Larsson S, Englund M, Struglics A, Lohmander LS. Interleukin-6 and tumor necrosis factor alpha in synovial fluid are associated with progression of radiographic knee osteoarthritis in subjects with previous meniscectomy. *Osteoarthritis and Cartilage*. 2015;23(11):1906-1914.
6. Vexler A, Tao G, Chen X. A toolkit for clinical statisticians to fix problems based on biomarker measurements subject to instrumental limitations: from repeated measurement techniques to a hybrid pooled-unpooled design. *Methods Mol Biol*. 2015;1208:439-460.
7. Plsikova Matejova J, Spakova T, Harvanova D, et al. A Preliminary Study of Combined Detection of COMP, TIMP-1, and MMP-3 in Synovial Fluid: Potential Indicators of Osteoarthritis Progression. *CARTILAGE*. 2021;13(2_suppl):1421S-1430S.