NYU Langone Orthopedics

NYU Langone Health

Age-Dependent Variation in Cytokine Type and Concentration in Knee Synovial Fluid Following Meniscal Injury

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Faculty Disclosures

Eric Strauss:

- AAOS (Board or committee member)
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Background

- Meniscal injury triggers an inflammatory response mediated by intra-articular cytokines and growth factors collectively termed **biomarkers**
- These biomarkers have been associated with cartilage degradation and progression to post-traumatic osteoarthritis (PTOA)
- The role of **age** in this inflammatory response is unclear

Purpose: to investigate age-dependent variation in cytokine types and concentration in knee synovial fluid following meniscal injury

Methods: Study Design

- Patients undergoing arthroscopic knee surgery for isolated meniscal injury were prospectively enrolled (2011 – 2024)
- Exclusion: systemic inflammatory/autoimmune disease, intra-articular injection < 3 months pre-op, immunomodulatory drug administration < 1 year pre-op
- Synovial fluid was aspirated from the operative knee prior to surgical incision
- The concentrations of 10 biomarkers of interest (RANTES, IL-6, MCP-1, MIP-B, VEGF, TIMP-1, TIMP-2,IL-1RA, MMP-3, and bFGF) were measured by immunoassay
- Those > 9 years following surgery completed VAS pain, Lysholm, Tegner, and KOOS-PS patient-reported outcome (PRO) surveys

Methods: Statistical Analysis

- **Age vs. each biomarker**
  - Multivariable linear regression (covariates: sex, BMI, baseline Outerbridge grade, symptom duration)
  - Conditional process analysis (moderator: symptom duration, mediator: baseline Outerbridge grade)
- Age vs. PROs (covariates: sex, BMI)
- Biomarkers vs. PROs (covariates: age, sex, BMI)
- Lysholm MCID-based responder analysis

Results: Cohort Demographics

Demographics	Biomarker Analysis (n = 160)	10-year PRO Analysis (n = 47)	MCID Analysis (n = 39)
Age (years) (mean ± SD)	50.2 ± 12.5	51.0 ± 11.7	50.1 ± 11.4
Sex (% male [95% CI])	53.8% [46.0 – 61.5]	30.1 ± 6.0	30.3 ± 6.2
Body mass index (kg/m^2) (mean ± SD)	29.1 ± 5.6	48.9% [34.6 – 63.2]	46.2% [31.6 – 61.4]
Follow-up time (years) (mean ± SD)	--	10.2 ± 1.3	9.1 ± 1.1

Results: Age vs. Biomarkers

Multivariable Linear Regression: Age vs. Biomarkers

Biomarker	β_{age} (standardized)	P-value
RANTES	- 0.096	0.277
IL-6	**+ 0.232**	**0.007***
MCP-1	+ 0.161	0.066
MIP-B	+ 0.067	0.440
VEGF	- 0.042	0.605
TIMP-1	+ 0.020	0.813
TIMP-2	+ 0.030	0.725
IL-1RA	+ 0.159	0.068
MMP-3	- 0.005	0.957
bFGF	- 0.133	0.134

- **Age** was positively associated with the concentration of **IL-6** when controlling for sex, BMI, symptom duration, and baseline Outerbridge grade

Results: Conditional Process Analysis

	Modifying Effect of Symptom Duration on Age (Age*Symptom Duration)		Symptom Duration Conditional Effect Significance Threshold (months)	Indirect Effect of Age through Baseline Outerbridge Grade [95% CI]
	β	P-value		
RANTES	- 0.0001	0.7947	--	0.0000 [-0.0044, 0.0043]
IL-6	**+ 0.0012**	**0.0014**	**> 5.24**	+ 0.0009 [-0.0036, 0.0057]
MCP-1	+ 0.0003	0.2223	--	+ 0.0018 [-0.0016, 0.0050]
MIP-B	+ 0.0005	0.0719	--	**+ 0.0038 [0.0007, 0.0075]**
VEGF	**+ 0.0008**	**0.0071**	**> 17.18**	**+ 0.0045 [0.0007, 0.0085]**
TIMP-1	+ 0.0001	0.7330	--	**- 0.0042 [-0.0078, -0.0010]**
TIMP-2	- 0.0001	0.8108	--	**- 0.0085 [-0.0144, -0.0032]**
IL-1Ra	**+ 0.0007**	**0.0389**	**> 10.29**	- 0.0021 [-0.0068, 0.0021]
MMP-3	0.0006	0.0516	--	**+ 0.0057 [0.0020, 0.0102]**
bFGF	-0.0006	0.0649	--	+ 0.0006 [-0.0032, 0.0046]

- **Moderator analysis**: age was positively associated with IL-6, VEG-F, and IL-1Ra in more chronic meniscal injuries
- Age was positively associated with the chosen mediator of baseline Outerbridge grade ($p < 0.001$, $\beta = + 0.0469$)
- **Mediator analysis:** age had significant positive indirect effect on MIP-B, VEGF, and MMP-3 and negative indirect effect on TIMP-1 and TIMP-2

Results: Age and Biomarkers vs. PROs

- Age at surgery was negatively associated with 10-year Tegner score ($p = 0.002$, $B = -0.445$) controlling for sex and BMI
- TIMP-1 concentration was positively associated with KOOS-PS ($p = 0.013$, $B = 0.346$) controlling for age, sex, and BMI
- **Lysholm MCID-based responder analysis**: treatment responders exhibited higher TIMP-1 than non-responders ($p = 0.031$)
- There were no other significant associations between age/biomarkers and PROs

Conclusions

- Age at surgery was associated with higher concentrations of several pro-inflammatory biomarkers (IL-6, VEGF, MIP-B, MMP-3) and lower concentrations of two key anti-inflammatory biomarkers (TIMP-1 and TIMP-2) in the synovial fluid prior to meniscus surgery
- Pre-operative anti-inflammatory markers were associated with improved long-term PROs
- These findings suggest an age-related intensification of the pro-inflammatory response and inhibition of the anti-inflammatory response that may contribute to the long-term functional decline seen in older patients after meniscus surgery
- Age-specific immunomodulatory therapeutic strategies should be further investigated to manage inflammation and mitigate progression forward post-traumatic osteoarthritis in older patients

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