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Day of Surgery Serum MMP-3 Concentration is Independently Associated with Achieving a KOOS4 and IKDC Patient Acceptable Symptom State 6 Years After Anterior Cruciate Ligament Reconstruction

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Disclosures

- **Lachlan Batty**: Consultant for Arthrex, presentations for Smith and Nephew, Arthrex, Device Technologies. Fellowship support Smith and Nephew
- **Kate E. Webster**: Nil
- **Natasha Vasileff**: Nil
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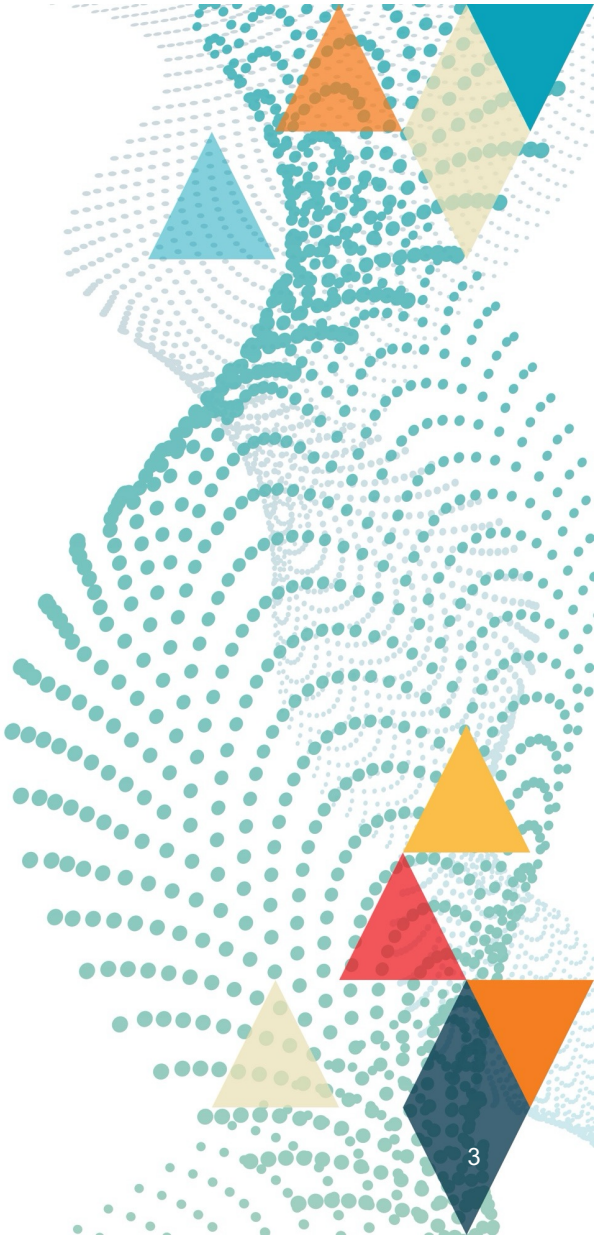
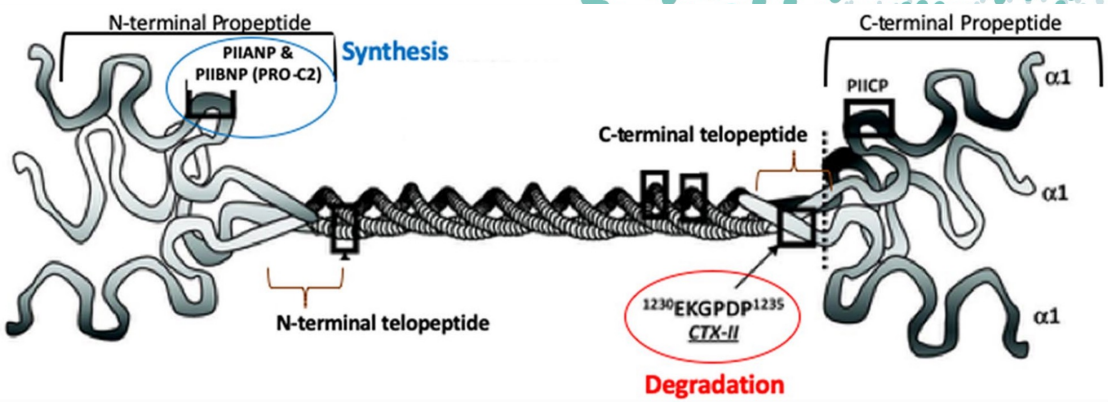
Background and Aims

- The risk of post traumatic arthritis is elevated after anterior cruciate ligament (ACL) injury. This can influence mid and long term patient reported outcome measures (PROMs).[1,2]
- Biomarkers of chondral metabolism and matrix remodelling may represent a means of quantitatively evaluating the post traumatic arthritis pathological process.[3]
- The aim of this study was to assess for a longitudinal association between three systemic biomarkers of chondral metabolism measured on the day of surgery and poor PROM scores at 6-year after primary ACL reconstruction.



Methods

- Prospective longitudinal study of 683 patients undergoing primary ACL reconstruction
- Urine and serum samples taken immediately prior to surgery
- Concentrations of 3 biomarkers of chondral or matrix metabolism were measured using immunoassays
  - Urinary C-terminal cross-linked telopeptide of type II collagen (CTX-II)
    - A marker of type 2 collagen degradation
  - Serum N-propeptide of collagen IIA (PIIANP)
    - A marker of type 2 collagen synthesis
  - Serum Matrix Metalloproteinase 3 (MMP-3)
    - Mediator in chondral matrix degradation.



Type 2 Collagen (Karsdal et al, 2009, Biomarkers 14(3):181-202)

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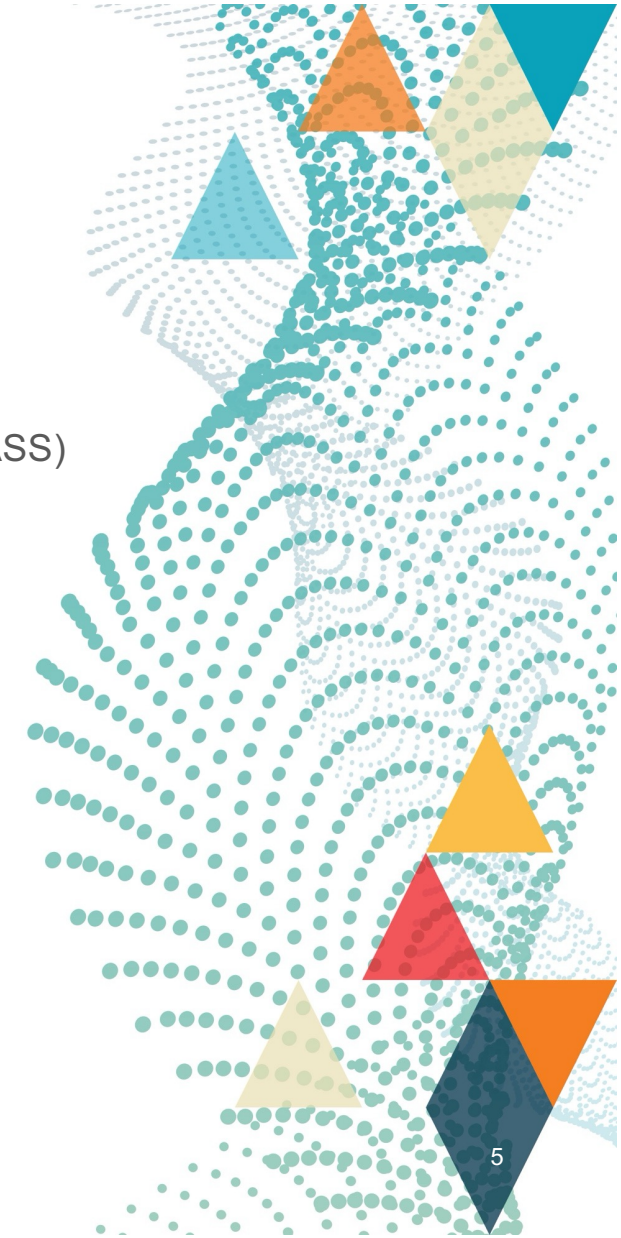
Methods

- Patient reported outcome scores (PROMS) were recorded at 6 years post operatively
  - International Knee Documentation Committee Subjective Knee Form (IKDC)
  - Knee Osteoarthritis and Outcome Score 4 (KOOS4)

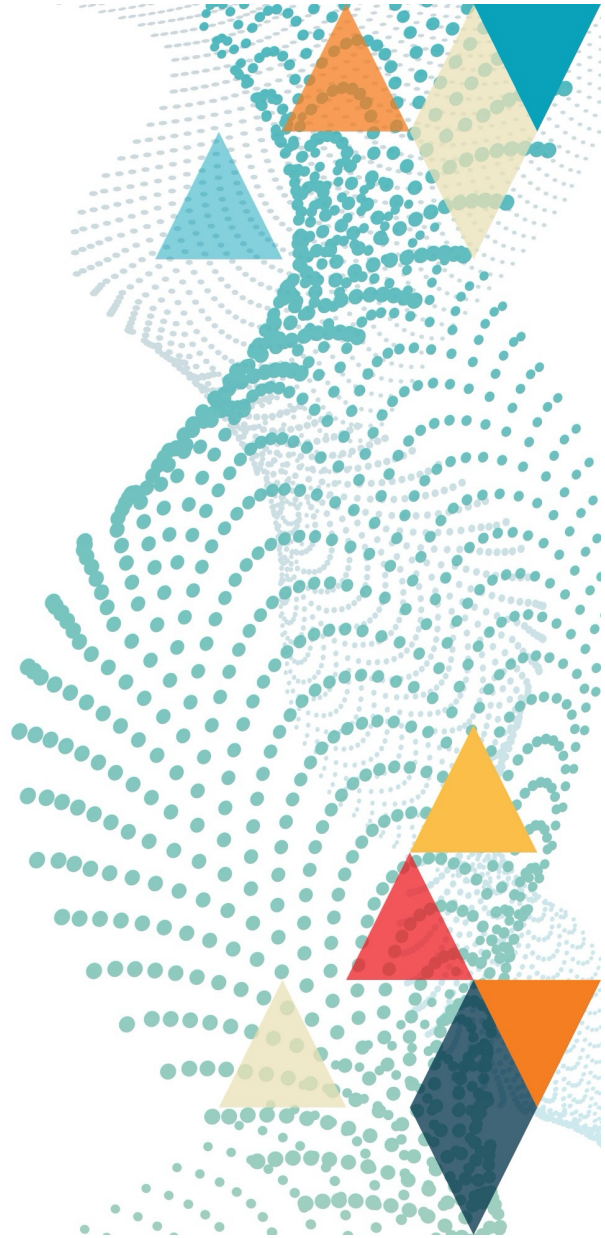
- PROM scores were dichotomised based on the patient acceptable symptoms state (PASS)
  - 79 used as the PASS for KOOS4[4]
  - 75.9 used as the PASS for the IKDC[5]

- Response rates
  - 683 patients in the longitudinal study
  - 440 (64.4%) had 6-year post operative PROM data
  - For the patients without 6-year PROM data
    - 92 patients (13.5%) had 5-year PROMs data carried forward for analysis
    - 34 patients (5.0%) had 4-year PROMs data that was carried forward for analysis
  - 566 (82.9%) of patients had an eligible PROM score included for analysis



Statistical Analysis

- Univariate and multivariable logistic regression models were created
  - 6-year IKDC and KOOS-4 PASS thresholds as the dependent variables
  - Biomarker concentrations as well as 11 other demographic and surgical variables were used as explanatory variables:
    - MMP3, PIIANP, CTX-II
    - Age
    - Sex
    - BMI
    - Articular cartilage score
    - Pre-operative Marx Activity Score
    - Time from Injury to Surgery
    - Prior contralateral ACL injury
    - Medial meniscal injury
    - Lateral meniscal injury
    - Lachman grade
    - Pivot shift grade
  - Patients with outlier biomarker values (quartile 3 plus 1.5 x IQR) were excluded
  - Patients with any missing data point were excluded



Results – Patients

660 patients provided biomarker samples

- 503 patients had biomarker AND 6-year PROM data
- 411 (Univariate) and 358 (Multivariate) patients included in KOOS4 analysis (after exclusion of patients with outlier biomarker values and any covariate data missing)
- 419 (Univariate) and 365 (Multivariate) patients included in IKDC analysis (after exclusion of patients with outlier biomarker values and any covariate data missing)

DEMOGRAPHIC	
Age at surgery (years), mean (SD)	25.02 (7.20)
Sex, Male, Female, n (%)	387 (60%), 255 (40%)
Pre-operative BMI, mean (SD)	24.60 (3.34)
Time from injury to surgery (days)	
Mean (SD)	226.06 (755.80)
Median (IQR)	58.00 (91.00)
Time from injury to surgery (stratified)	
0 to 3 weeks	68 (11%)
3 weeks to 3 months	353 (55%)
3 months to 12 months	155 (24%)
12 months +	66 (10%)
Graft type	
Hamstring tendon, n (%)	567 (88%)
Quadriceps Tendon, n (%)	53 (8.3%)
Patellar Tendon, n (%)	21 (3.1%)
LARS, n (%)	1 (0.2%)
Lateral Extra Articular Tenodesis (modified Ellison), n (%)	10 (1.6%)
Previous contralateral ACL, n (%)	65 (10%)
Pre-operative Marx score, mean (SD)	12.33 (4.00)

DEMOGRAPHIC CONT.	
Articular Cartilage Grade	
Median (IQR, range)	0 (0-0, 0-15)
Mean (SD)	0.81 (1.86)
Medial Meniscus Status	
Intact, n (%)	461 (71.8%)
Torn, n (%)	173 (26.9%)
Previous Resection, n (%)	8 (1.2%)
Lateral meniscus status	
Intact, n (%)	416 (65%)
Torn, n (%)	226 (35%)
Lachman Grade	
0/1, n (%)	212 (33%)
2, n (%)	389 (61%)
3, n (%)	36 (5.7%)
Pivot Shift Grade	
0/1, n (%)	126 (20%)
2, n (%)	467 (73%)
3, n (%)	44 (6.9%)

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Results - Patients

PROM scores

N=503	Mean (SD)	Median (IQR)	Range (min, Max)
KOOS Pain	93.16 (9.27)	97.22 (11.11)	41.67, 100.00
KOOS Function Daily Living	96.89 (6.82)	100.00 (2.94)	47.06, 100.00
KOOS Quality of life	79.27 (19.25)	81.25 (25.00)	0.00, 100.00
KOOS Sport	89.83 (12.78)	95.00 (15.00)	25.00, 100.00
KOOS-4	86.68 (13.06)	90.89 (15.37)	24.11, 100.00
IKDC-SKF	87.74 (13.03)	91.95 (14.94)	36.78, 100.00

Baseline biomarker concentrations

n=503	Urine CTX-II, ng/mmol Cr	Serum PIIANP, ng/mL	Serum MMP-3, ng/mL
Mean (SD)	1,012.34 (1,279.13)	19.40 (9.29)	20.48 (14.84)
Median (IQR)	471.88 (908.97)	17.13 (13.14)	17.14 (18.24)
Min, Max	4.75, 6,263.35	1.38, 45.66	0.20, 73.56

Results – Logistic regression analysis, KOOS4

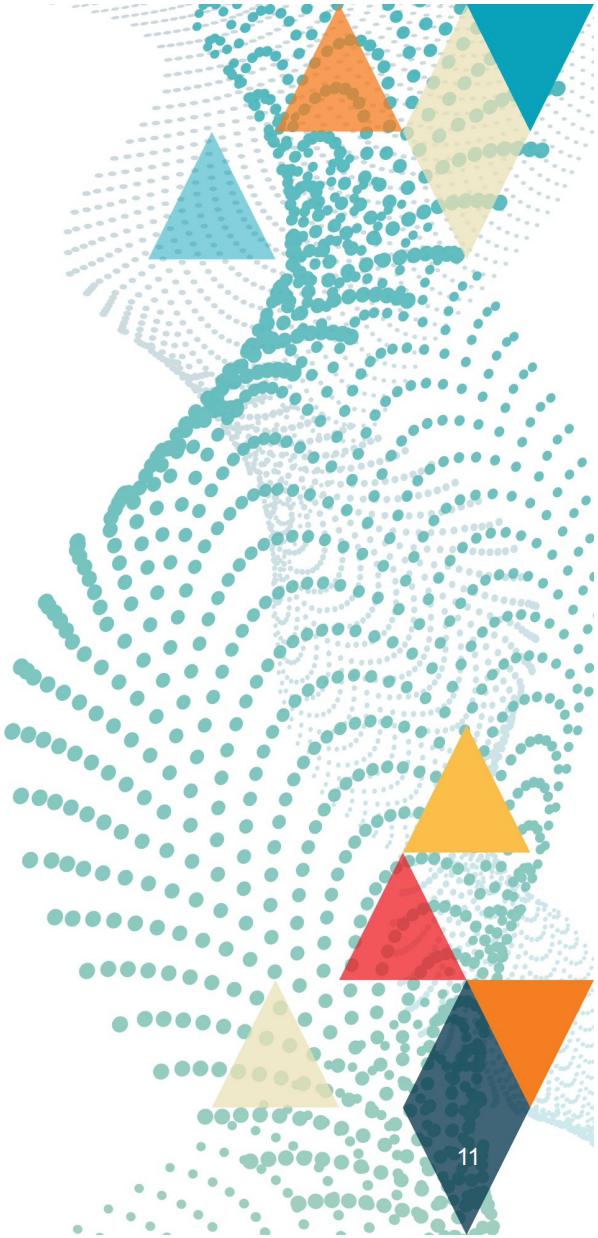
	Univariate				Multivariate			
Characteristic	N	OR	95% CI	p-value	N	OR	95% CI	p-value
Baseline s-MMP-3	411	0.98	0.97, 1.00	**0.022***	358	0.98	0.96, 1.00	**0.014***
Baseline s-PIIANP	411	1.02	1.00, 1.05	0.11	358	1.02	0.99, 1.06	0.14
Baseline u-CTX-II	411	1	1.00, 1.00	0.2	358	1	1.00, 1.00	0.4
Age	411	0.96	0.93, 0.99	**0.017***	358	0.98	0.93, 1.04	0.5
Articular Cartilage Score	411	0.86	0.77, 0.96	0.006*	358	0.89	0.77, 1.02	0.094
Preopoerative MARS	369	1.05	0.99, 1.11	0.13	358	1.02	0.94, 1.10	0.6
Time from injury to surgery	408	1	1.00, 1.00	0.2	358	1	1.00, 1.00	0.2
Preopoerative BMI	411	0.92	0.86, 0.98	**0.015***	358	0.92	0.85, 1.00	0.063
Sex								
Female	183	Ref	Ref		156	Ref	Ref	
Male	228	0.87	0.54, 1.41	0.6	202	1.03	0.56, 1.89	>0.9
Prior Contralateral ACL injury								
No	362	Ref	Ref		317	Ref	Ref	
Yes	49	0.7	0.36, 1.43	0.3	41	0.64	0.29, 1.51	0.3
Medial Meniscus								
Intact	289	Ref	Ref		259	Ref	Ref	
Not Intact	116	1.17	0.69, 2.04	0.6	99	1.41	0.74, 2.78	0.3
Lateral Meniscus								
Intact	267	Ref	Ref		230	Ref	Ref	
Not Intact	141	0.92	0.56, 1.52	0.7	128	1.03	0.58, 1.85	>0.9
Lachman Grade								
0 or 1	140	Ref	Ref		124	Ref	Ref	
2	248	0.84	0.50, 1.39	0.5	214	1.04	0.54, 1.96	>0.9
3	20	0.96	0.32, 3.54	>0.9	20	3.42	0.61, 24.1	0.2
Pivot Shift Grade								
0 or 1	87	Ref	Ref		78	Ref	Ref	
2	294	0.75	0.39, 1.36	0.4	254	0.52	0.23, 1.11	0.1
3	27	0.6	0.22, 1.74	0.3	26	0.33	0.07, 1.55	0.15

Results – Logistic regression analysis, IKDC

	Univariate				Multivariate			
Characteristic	N	OR	95% CI	p-value	N	OR	95% CI	p-value
Baseline s-MMP-3	419	0.98	0.97, 1.00	**0.017***	365	0.98	0.96, 1.00	**0.034***
Baseline s-PIIANP	419	1.03	1.00, 1.06	**0.038***	365	1.02	0.99, 1.06	0.2
Baseline u-CTX-II	419	1	1.00, 1.00	**0.043***	365	1	1.00, 1.00	0.8
Age	419	0.95	0.92, 0.98	**0.001***	365	0.96	0.91, 1.02	0.2
Articular Cartilage Score	419	0.86	0.78, 0.96	**0.005***	365	0.9	0.79, 1.02	0.1
Preopoerative MARS	376	1.08	1.02, 1.15	**0.007***	365	1.05	0.97, 1.14	0.2
Time from injury to surgery	416	1	1.00, 1.00	0.083	365	1	1.00, 1.00	0.12
Preopoerative BMI	419	0.89	0.83, 0.96	**0.001***	365	0.91	0.83, 0.99	**0.024***
Sex								
Female	184	Ref	Ref		156	Ref	Ref	
Male	235	0.69	0.41, 1.12	0.14	209	0.85	0.44, 1.62	0.6
Prior Contralateral ACL injury								
No	370	Ref	Ref		324	Ref	Ref	
Yes	49	0.63	0.33, 1.30	0.2	41	0.58	0.26, 1.40	0.2
Medial Meniscus								
Intact	297	Ref	Ref		266	Ref	Ref	
Not Intact	116	1.41	0.80, 2.56	0.2	99	2.21	1.10, 4.74	**0.033***
Lateral Meniscus								
Intact	272	Ref	Ref		234	Ref	Ref	
Not Intact	144	0.79	0.48, 1.31	0.3	131	0.77	0.43, 1.39	0.4
Lachman Grade								
0 or 1	143	Ref	Ref		126	Ref	Ref	
2	253	1.18	0.71, 1.95	0.5	219	1.47	0.76, 2.83	0.3
3	20	1.57	0.49, 7.02	0.5	20	5.38	0.82, 48.3	0.1
Pivot Shift Grade								
0 or 1	90	Ref	Ref		81	Ref	Ref	
2	299	1.02	0.55, 1.81	>0.9	258	0.49	0.22, 1.04	0.07
3	27	1.1	0.39, 3.63	0.9	26	0.41	0.08, 2.33	0.3

Conclusions

- Increasing serum MMP-3 levels as measured on the day of surgery were independently associated with failing to achieve the IKDC and KOOS4 PASS at 6 years after ACL reconstruction
  - For every additional ng/mL increase in serum MMP-3 at baseline, there was a 2% reduction in the odds achieving the IKDC or KOOS4 PASS threshold
- Urinary CTX-II and serum PIIANP were not found to have any such association in the multivariate modelling
- This day of surgery blood test may be helpful in identifying patients at risk of a poor outcome 6 years after ACL reconstruction



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