Changes In Synovial Fluid Markers In Osteoarthritis Are Associated With Changes In Gait Biomechanics After High Tibial Osteotomy

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Disclosures

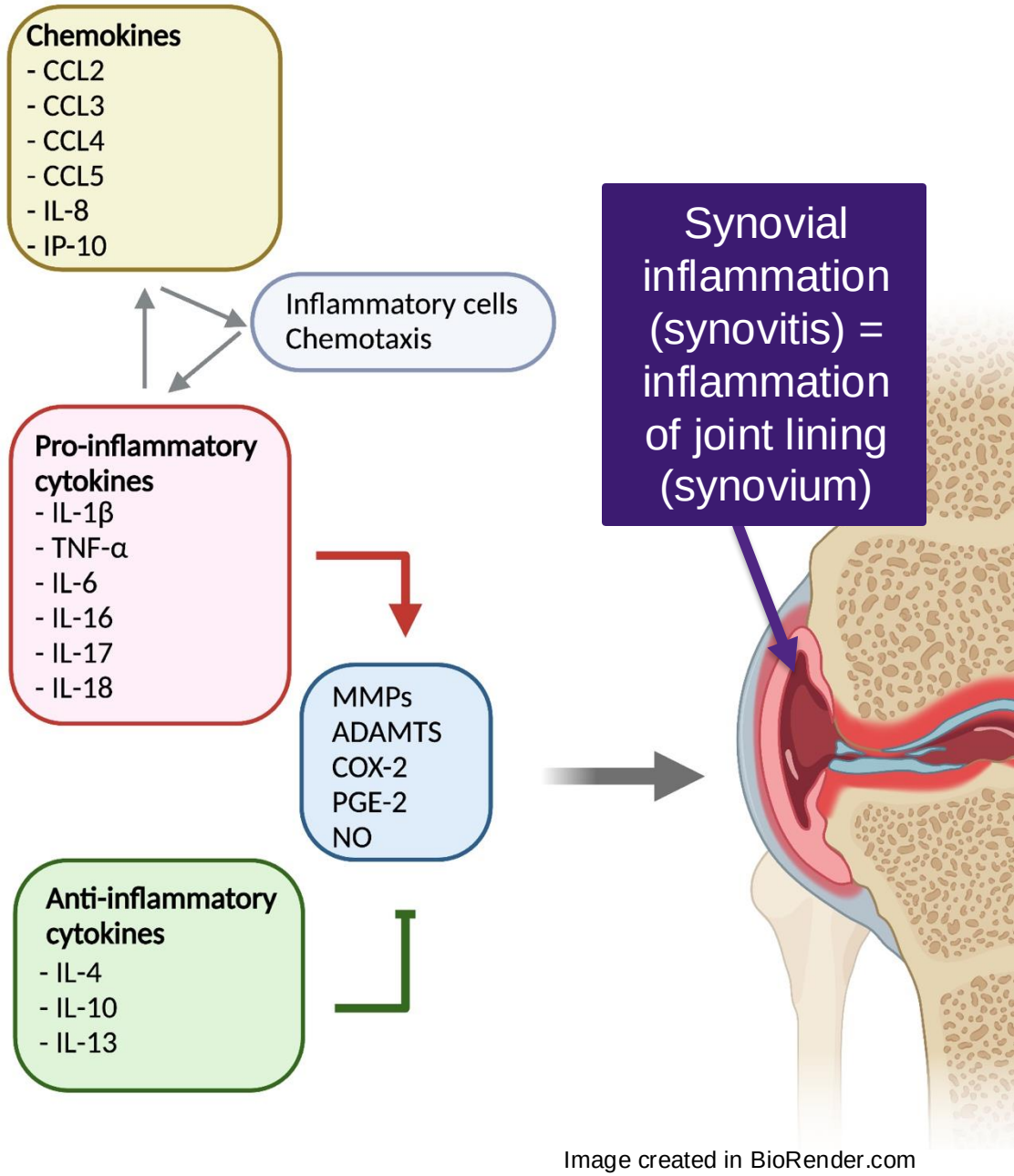
- Nothing to disclose

Inflammation in Osteoarthritis (OA)

- Mechanisms driving inflammation are <u>complex</u>, multiple pathways
  - Pleiotropic effects depending on context

- Associated with:
  - Clinical symptoms (swelling, pain)[1-3]
  - Radiographic severity[4]
  - Onset and progression of structural joint changes[5,6]
  - Risk of knee replacement

- Important to further understand <u>mechanisms of synovitis in OA</u> → therapeutic targets



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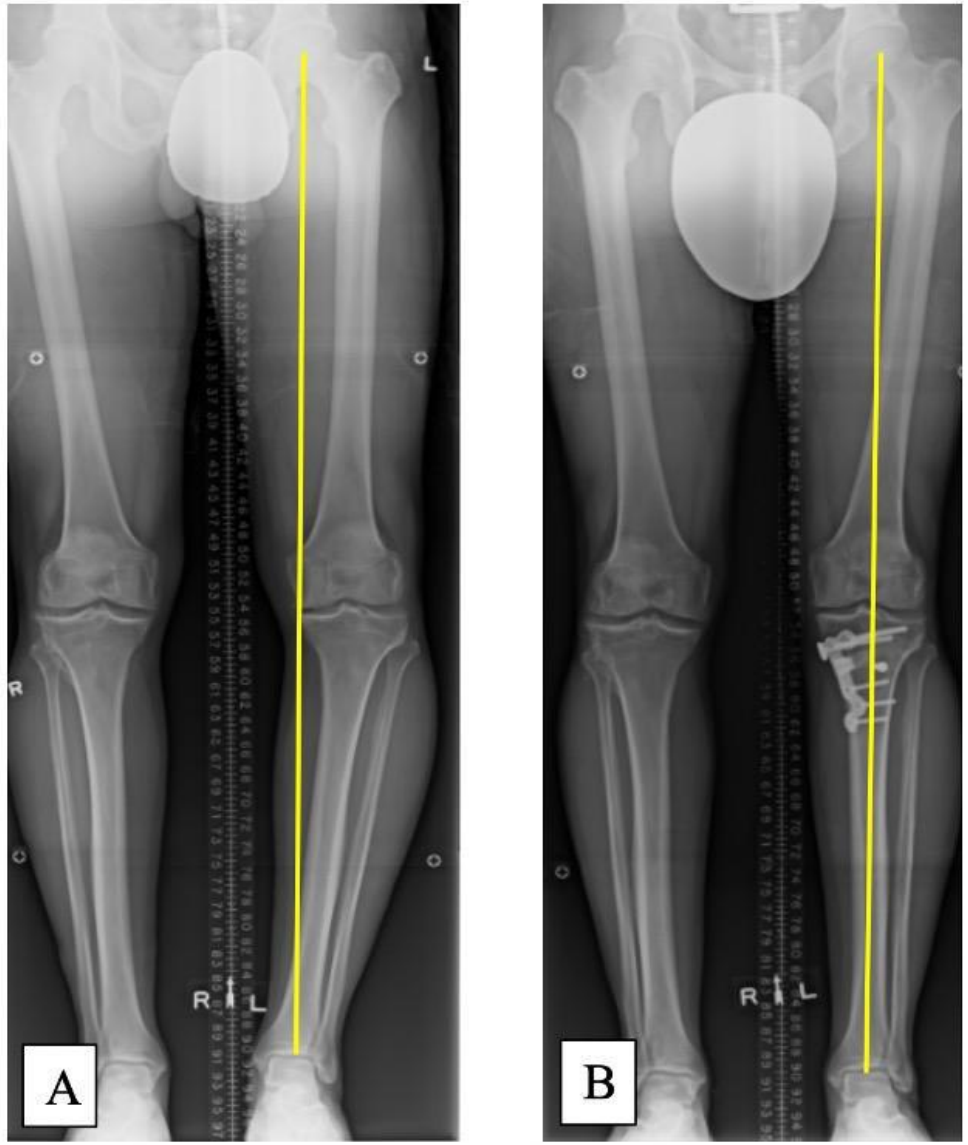
High Tibial Osteotomy (HTO)

- Leads to:
  - Reduction in knee adduction moment (KAM)[7-9]
  - Increased walking speed, stride length[9]
  - Improvements in clinical outcomes (pain, function)[7,10]
  - Potential delayed time to knee replacement[11]

- Unknown how altered loading affects inflammatory pathophysiology



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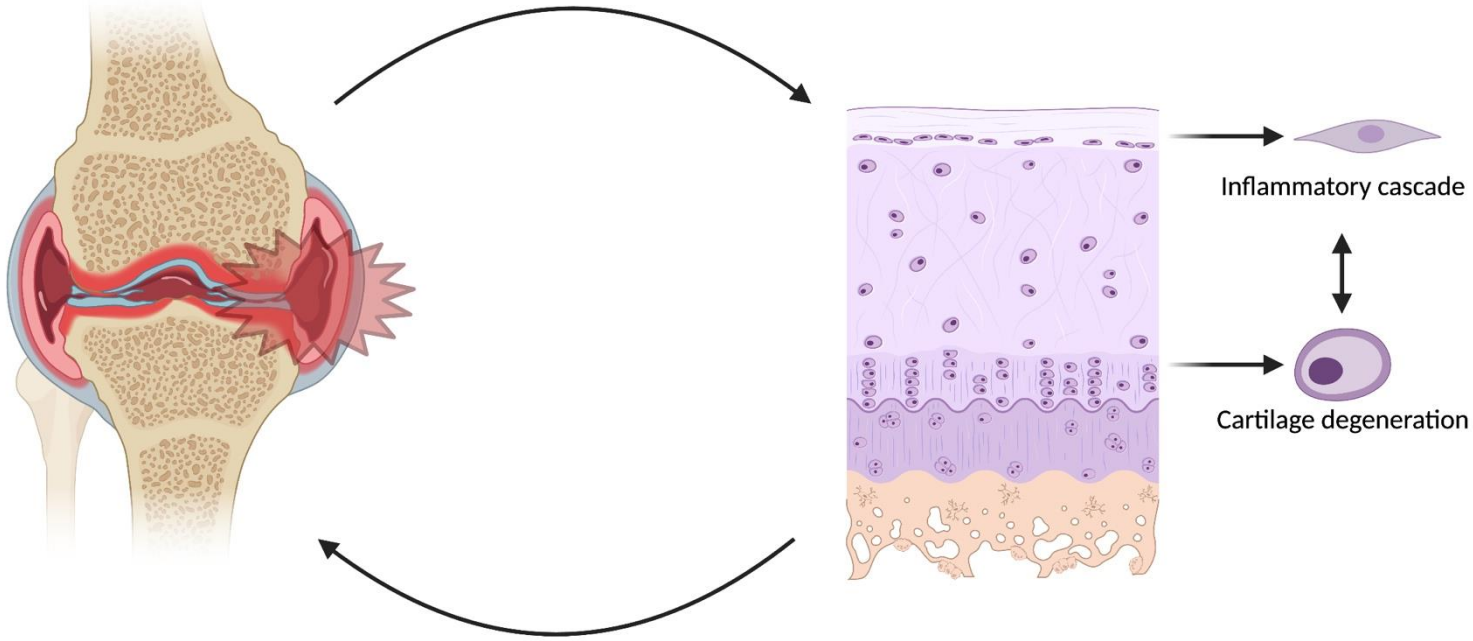
Mechanoinflammation

- Link between mechanical loading and inflammation
  - Association between decrease in medial load and effusion-synovitis post-HTO[12]
  - Synovial perivascular edema is associated with altered gait patterns[13]
  - Changes in synovial fluid biomarkers after joint realignment[14-16]

- <u>Changes in joint mechanics may lead to changes in joint biochemistry and inflammation</u>



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Gap

- Although mechanobiological processes are thought to be integral to knee OA pathogenesis and potential interventions, it is unclear if altering gait mechanics can alter joint biology

Objective

- Explore the associations between observed changes in synovial fluid biomarkers and changes in gait

Methods

- **3D Gait analyses**
  - Knee adduction moment, knee flexion moment

- **Synovial fluid biomarkers**
  - Gene set enrichment analysis + leading edge analysis
  - Top positively enriched (higher after HTO): **EGF, PDGF-BB, FGF-2**
  - Top negatively enriched (higher at baseline): **IL-6, TNF-α, IL-1β**
  - Categorized as responders vs non-responders
    - **Responder** = decreased (negatively enriched) or increased (positively enriched) after HTO

Statistical Analyses

- Mixed effects polynomial regression models: compare external knee moments (outcome) between responders and non-responders over 100% of stance (predictor)
  - Adjusted for height, weight, gait speed and KL grade

Characteristic	Participants (n=26)
Sex, male	21 (81%)
Age, years	53.9 ± 5.4
BMI (kg/m^2)	30.2 ± 4.2
MAA, (degrees)	-6.4 ± 2.3
KL grade	
1	3 (11%)
2	7 (27%)
3	16 (62%)
OARSI medial narrowing	
1	5 (20%)
2	10 (40%)
3	10 (40%)
OARSI lateral narrowing	
0	20 (80%)
1	5 (20%)
KOOS Pain	51.7 ± 12.9
KOOS ADL	63.4 ± 16.0
KOOS Symptoms	49.3 ± 12.4
KOOS Sport	32.6 ± 23.2
KOOS QoL	25.0 ± 15.0

Results: Mean Changes

Anti-inflammatory

Pro-inflammatory

In general, there was a larger increase in anti-inflammatory and decrease in pro-inflammatory biomarkers concentration in the responder group after HTO .

Biomarker	Group (n)	Mean change ± SD (FI units)
EGF	All (26)	28.48 ± 102.12
	Responders (17)	46.18 ± 123.78
	Non-responders (9)	-4.93 ± 4.84
PDGF-BB	All (26)	278.75 ± 27.68
	Responders (14)	557.82 ± 1060.28
	Non-responders (12)	-46.84 ± 43.46
FGF-2	All (26)	27.68 ± 439.30
	Responders (17)	129.82 ± 419.83
	Non-responders (9)	-165.24 ± 431.88
IL-6	All (26)	-895.02 ± 4708.07
	Responders (18)	-2030.75 ± 4959.40
	Non-responders (8)	1914.23 ± 2530.62
TNF-α	All (26)	-140.85 ± 612.26
	Responders (17)	-245.95 ± 740.76
	Non-responders (9)	50.66 ± 78.70
IL-1β	All (26)	-4.85 ± 26.02
	Responders (17)	-13.05 ± 26.52
	Non-responders (9)	13.69 ± 17.19

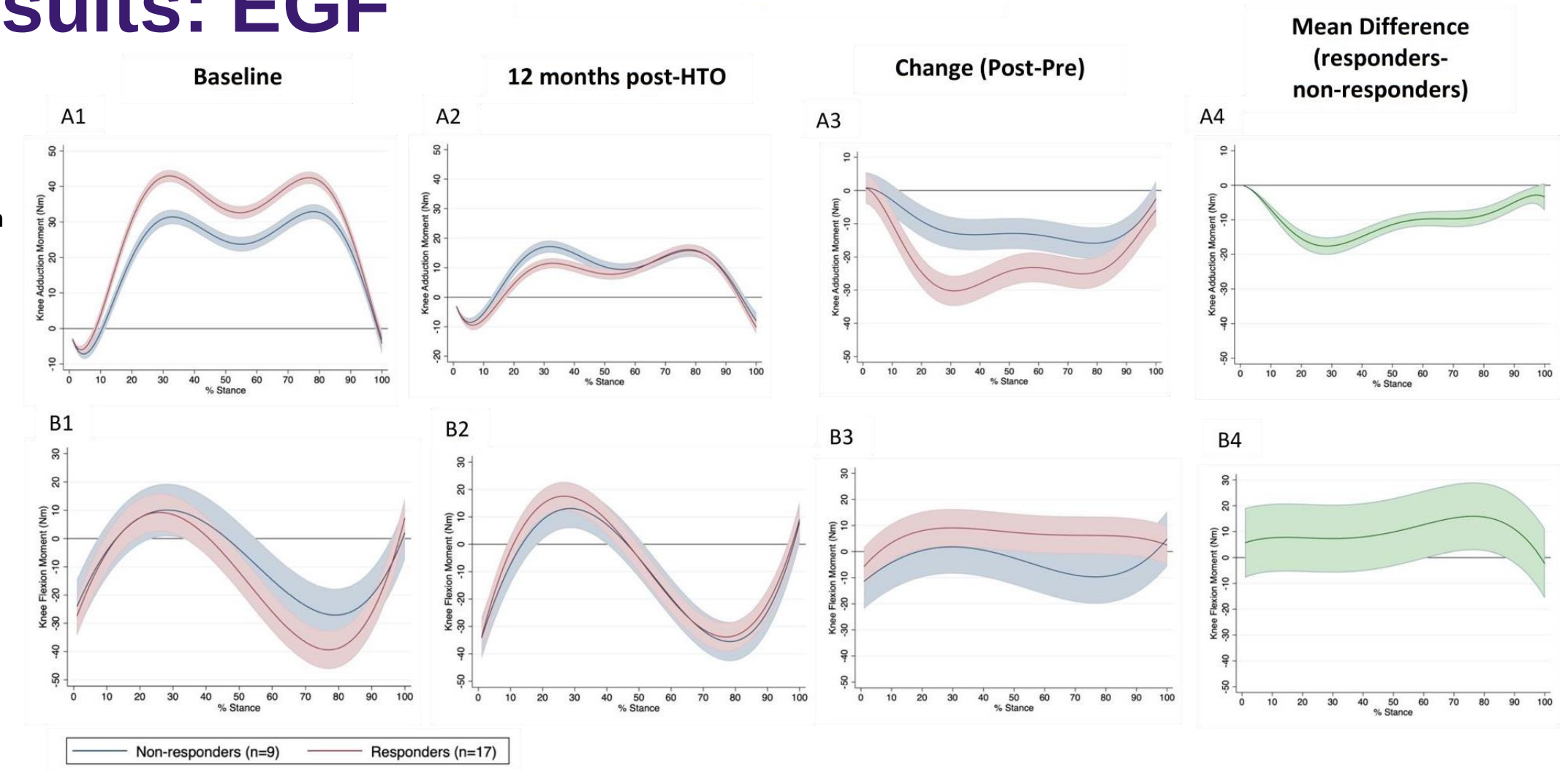
Results: Polynomial Regression

	% Of stance that differs	Point in stance with greatest difference (Nm [95% CI])
EGF ; KAM	0-97%	28% (-17.62 [-20.08; -15.08])
EGF ; KFM	62-86%	76% (15.90 [2.84; 28.96])
PDGF-BB ; KAM	0-92%	71% (5.01 [3.14; 7.86])
PDGF-BB ; KFM	75-90%	83% (13.36 [1.05; 25.66])
FGF-2 ; KAM	0-97%	75% (-11.63 [-14.09; -9.18])
FGF-2 ; KFM	ND	77% (-11.74 [-24.94; 2.46])
TNF-α ; KAM	20-94%	72% (-9.97 [-12.42; -7.53])
TNF-α ; KFM	ND	37% (6.65 [-6.20; 19.49])
IL-6 ; KAM	1-91%	30% (12.89 [10.29; 15.18])
IL-6 ; KFM	11-96%	31% (21.34 [7.28; 34.36])
IL-1β ; KAM	39-87%	62% (-8.17 [-10.32; -6.02])
IL-1β ; KFM	73-88%	82% (-13.82 [-26.08; -1.57])

Polynomial regression results comparing change in gait parameters between responders and non-responders.

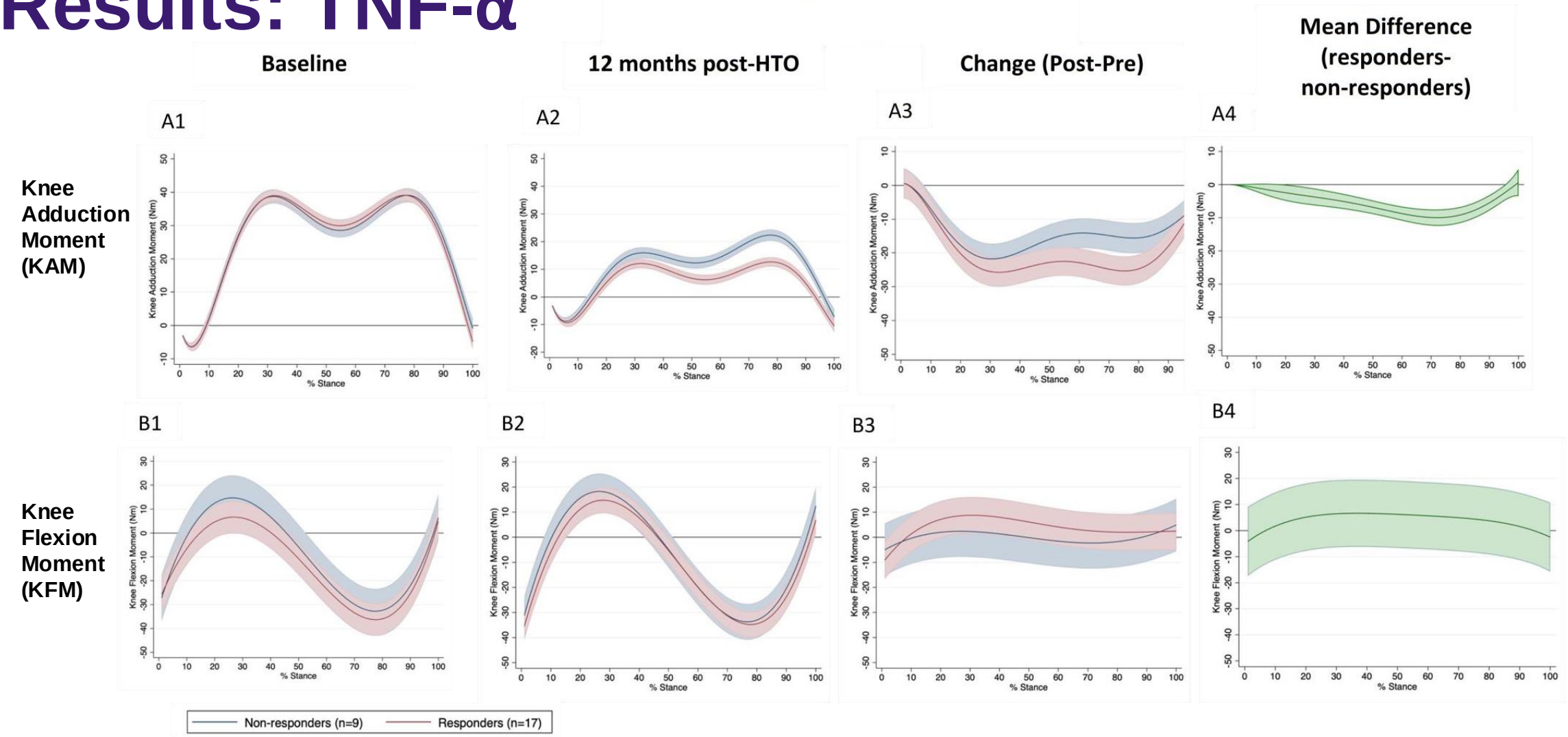
Greater decrease in KAM for EGF, FGF-2, TNF-α and IL-1β in the responder groups.
Greater increase in KFM for EGF, PDGF-BB and IL-6 in the responder groups.

Results: EGF



Greater decrease in KAM (greatest corresponding to a decrease in 1st peak KAM).
Greater increase in KFM (greatest corresponding to a decrease in peak KEM).

Results: TNF-α



Greater decrease in KAM (greatest corresponding to a decrease in 2nd peak KAM). No difference in KFM.

Conclusions

- After HTO:
  - The responders in EGF, FGF-2, TNF-α and IL-1β had greater decreases in KAM
  - The responders in EGF, PDGF-BB and IL-6 had greater increases in the KFM

This suggests a biological response after HTO that is associated with greater **decreases in KAM** and **increases in KFM** during walking.

These findings are consistent with the ability to alter **mechanobiological processes** in patients with OA.

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