

RELATIONSHIPS BETWEEN CARTILAGE MRI MARKERS, BIOCHEMICAL MARKERS, AND PAIN

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Objective

Basic Observations:

- For OA patients, pain is a very central symptom
- There is limited understanding of the structural changes that result in pain. Therefore, treatment development is challenging
- Pain quantification is problematic, so surrogate markers are desirable

Objective:

- *To investigate the association to pain for a set of imaging cartilage markers and biochemical cartilage/bone markers*

OA Pathogenesis: Pain?

	Healthy	Biomechanical stress alterations	Internal structure changes	Surface structure alterations	Fibrillation & Cartilage loss	Denudation & Cartilage loss
Cart.						
Bone						
Pain:	No?	?	?	?	?	Yes?

Methods: Study Population

We enrolled 159 subjects and included those above 30 and taking no pain medication within 48 hours of the follow-up visit (after 21 months), in total 123 subjects completed:

- Age: 58±14
- Gender: 47% female
- BMI: 26±4
- 54% with rOA (KL>0 at baseline)

Methods: Overview

Measurements:

- Knee radiographs were acquired in a semi-flexed load-bearing position using the SynaFlex gave Kellgren & Lawrence (KL) score and joint space width (JSW)
- Biochemical markers
- Knee MRI cartilage markers
- Pain

Methods: Biochemical Markers

CTX-II: Cartilage degradation
MMP mediated type II collagen degradation measured by urine CTX-II (C-terminal telopeptide of type II collagen) using the CartiLaps ELISA assay and corrected for urinary creatinine levels.

CTX-I: Bone resorption
Cathepsin K mediated type I collagen degradation measured by serum CTX-I.

Methods: MRI Cartilage Markers

From MRI, we focus on markers of cartilage quality and morphometry:

Healthy | Bio-mechanical stress | Internal structure changes | Surface structure alterations | Fibrillation & Cartilage loss | Denudation

Cartilage

MRI Markers: Curvature, Homogeneity, Smoothness, Thickness, Volume

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Methods: Automatic Quantification from MRI

0.18 T, 3D T1 → Smoothness, Homogeneity → Volume, Thickness, Curvature

Folkesson, Dam et al. 2007 Trans Medical Imaging
 Dam et al. 2008 Medical Image Analysis
 Dam, Folkesson et al. 2007 Osteoarthritis & Cartilage
 Qazi, Dam, Karsdal et al. 2007 Osteoarthritis & Cartilage

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Methods: Pain Quantification - VAS

Assumption: no pain medication within 48 hours

Pain was quantified using a visual assessment scale (VAS) for answering the question "What was your level of pain in the last 24 hours?"

No Pain ————— Most pain

Pain was then recorded as 0-100 mm.

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Results: Relationships to Pain at Follow-up

All MRI markers were measured in the medial tibio-femoral compartment.

r: linear correlation with significance by Pearson's test
 p: Wilcoxon rank sum test for pain vs no pain groups
 OR: Odds ratio for having pain with groups split at marker median
 adj: Adjusted for age and gender

	Cross-sectional			Longitudinal		
	r	p	OR	r	p	OR
BMI	0.26*	0.021*	3.3*	-0.10	0.288	1.9
JSW	-0.19	0.062	3.1*	-0.09	0.737	1.3
CTX-I	-0.16	0.028*	2.9	0.09	0.129	2.3
CTX-II	0.29**	0.001**	7.1**	0.05	0.077	3.2*
Curvature	-0.02	0.549	1.4	0.06	0.973	0.7
Homogeneity	0.22*	0.090	2.3	0.20	0.043*	3.3*
Smoothness	-0.13	0.936	0.9	-0.05	1.000	1.1
Thickness	-0.19	0.425	1.3	-0.14	0.866	0.9
Volume	-0.13	0.681	1.5	-0.16	0.063	2.3
CTX-II adj.	0.28**	0.003**	7.1**	0.05	0.077	3.2*
Homogeneity adj.	0.23*	0.099	2.3	0.20	0.043*	3.3*

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Results: Loss of Internal Cartilage Structure

Loss of internal cartilage structure (homogeneity change over 21 months) predicted pain at follow-up for a large sub-population.

Useful for study population design?

OR for Pain

Tertiles of Δ Homogeneity

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Aside / Future Work: Combining Biochemistry & MRI

OARSI 2007: Cartilage Longevity (linear combination of CTX-II and MRI markers) gave superior prediction of radiographic progression

Which combination will be optimal for predicting pain in clinical studies?

OR for Progression

Quartiles

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Conclusion

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Pain was associated with

- Cartilage breakdown (CTX-II) rather than bone turnover (CTX-I)
- Cartilage structure (homogeneity) rather than denudation (volume/thickness)



The results need to be validated in a larger, independent population – possibly searching for causality links.

Take home message:

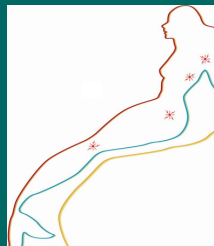
When exploring pain prevention, don't ignore early stage cartilage degradation!

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13/13

Thank you for your attention ...

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Logo from the 2006 MICCAI Joint Disease Workshop

A Danish OA case study:

Even for a little mermaid, sitting 95 years on a rock in the cold waters of Copenhagen eventually leads to joint stiffness.

However, pain quantification is problematic due to lack of patient responsiveness.

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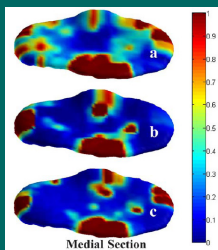
Search for Causality: Is Pain Focal?

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Which (continuous) ROI allows the smallest sample size for a given biomarker?

In medial, tibial compartment for diagnostic markers for homogeneity (a), volume (b), and thickness (c); the illustrated ROIs reduce the required sample sizes 20-50%.

For homogeneity, no ROI related to pain – pain was not focal.



Qazi, Dam, Nielsen
IEEE TMI (in review)

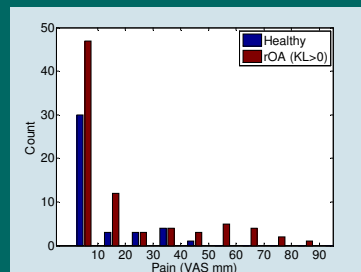
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Results: Pain Levels

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Many have no pain.

Among those with pain, the pain is generally higher for the OA subjects.



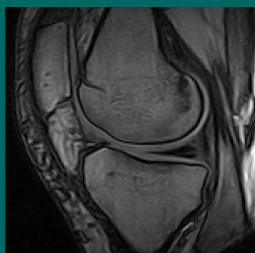
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Methods: MRI Scans

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Knee MR scans were acquired from a low-field 0.18T Esaote C-span scanner at BL and FU using a modified Turbo 3D T1 sequence:

- 40° flip angle
- TR 50 ms
- TE 16 ms
- Sagittal
- 0.7 × 0.7 × 0.8 mm³
- Scan time 10 min



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