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Can imaging improve outcome in OA?

OP0197

EVALUATING THE RELATION OF STRUCTURAL DAMAGE BY MRI TO CLINICAL PAIN SCORES, PAIN SENSITISATION AND TYPE II COLLAGEN DEGRADATION IN KNEE OSTEOARTHRITIS

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Background: The evolution of pain in relation to damage in the synovium, bone and cartilage in osteoarthritis (OA), coupled with their relation to wet biochemical markers are not well understood.

Objectives: In this study we evaluated the relation between structural damage by MRI, clinical and pain sensitisation measures and wet biochemical biomarkers in knee OA.

Methods: We recruited 130 participants fulfilling ACR criteria with advanced OA requiring total knee replacement (TKR) (n=80), mild OA having standard care (n=42) and non-OA controls (n=8). Knee MRI in 90 subjects (72 F, 18 M) was acquired and assessed by two radiologists with the MRI Knee Osteoarthritis Score (MOAKS). Overall MOAKS scores were created for Bone Marrow Lesions (BML), Cartilage Degradation (CD) and effusion/Hoffa synovitis (tSyn). Type II collagen cleavage products (CTX-II) were determined by ELISA. Clinical scoring was performed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for pain levels (WOMAC_P), Hospital Anxiety and Depression Scale (HADS), Body mass index (BMI) and pain sensitisation with pain pressure thresholds (PPT) of the patella by Quantitative Sensory Testing (QST).

Results: The mild OA group had a mean age of 63 +/-9 yr and the advanced OA group 69 +/-9 yr. The advanced OA group had higher levels of pain, with a mean WOMAC_P of 58 +/- 22 compared with the mild OA group who had a mean WOMAC_P of 40 +/-22. WOMAC_P correlated with the total number of regions with cartilage damage (nCD) (R=0.225, p=0.033) and total number of BMLs (nBML) (R=0.195, p=0.065) using BMI, age and HADS as covariates. Levels of CTX-II correlated with tSyn (R=0.313, p=0.03), nBML (R=0.252, p=0.019), number of osteophytes (R=0.33, p=0.002) and nCD (R=0.218, p=0.042), using BMI and age as covariates. The correlation for urinary CTX-II with tSyn (p=0.006) is shown in Figure 1 using a partial linear regression analysis of MOAKS, BMI and age. We also found CTX-II correlated with lesion load scores (total number of lesions multiplied by MOAKS size by% damage scores) for CD (R=0.277, p=0.009) and BML (r=0.308, p=0.004). PPT correlated with patella MOAKS scores for nBML (R=-0.221, p=0.038) and nCD (R=-0.279, p=0.009), with HADS, BMI and age as covariates.

Conclusion: There is a direct correlation between the degree of cartilage damage and BMLs with pain in OA. Type II collagen degradation products were higher when there was more severe MRI-detected synovitis, BMLs and cartilage damage in the knee joint, suggesting that the source of enzymes degrading type II collagen in OA, including matrix metalloproteinases, are also likely to be produced by synovium and bone (1) and not just cartilage, as previously hypothesised in other studies. There was also a correlation between pain sensitisation and frequency of BMLs and cartilage degradation, suggesting that molecular mediators of pain sensitisation, which we have shown are produced by BMLs (1), are a cause of patient-reported OA pain.

REFERENCES:

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Figure 1

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MRI-DETECTED STRUCTURAL ABNORMALITIES AND DEVELOPMENT OF INCIDENT RADIOGRAPHIC KNEE OSTEOARTHRITIS OVER 10 YEARS OF FOLLOW-UP

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Background: Structural joint pathology on MRI has been found in knees without radiographic evidence of osteoarthritis (OA). We have previously shown that structural abnormalities on MRI may be precursors of disease and associated with the detection of incident radiographic knee OA (ROA) up to 2 years later, and in some circumstances up to seven years later. The prognostic value of structural abnormalities on MRI for knee OA, however, is unknown.

Objectives: Estimate the probability of incident ROA over 10 years of follow-up, according to structural abnormalities detected on baseline MRIs.

Methods: A subcohort of participants (862 knees, one knee/person) from the Osteoarthritis Initiative (OAI) with at least one knee at risk of developing ROA (i.e., Kellgren-Lawrence (KL) 0,1 at baseline) was randomly selected. MRI-detected structural features of the knee were assessed by expert readers using the MRI Osteoarthritis Knee Score (MOAKS). Participants underwent bilateral posteroanterior fixed-flexion weight-bearing knee radiography at baseline and annually through year 4, and then every two years until year 10. Radiographs were centrally read for KL grade, with ROA defined as KL₂ or higher. Survival was estimated with the Turnbull non-parametric maximum likelihood estimator, a generalization of Kaplan Meier curves for interval censored data. Survival curves were compared using a log rank permutation test available in the R package interval. Hazard ratios were estimated using Cox models fit using the R package icenReg, designed for interval censored data. Features were considered one at a time, with no adjustments.

Results: Knees with any of the following structural abnormalities had higher estimated probabilities for the development of radiographic OA within two, four and 10 years of follow-up: effusion-synovitis, Hoffa-synovitis, bone marrow lesions in the medial compartment and whole knee, surface area and full thickness cartilage damage in the medial compartment and whole knee, and medial meniscal extrusion (Table 1). Differences in the probability for the development of ROA within two, four, and 10 years of follow-up were significant (pointwise 95% confidence intervals did not include 0), between knees without the abnormality and knees in the most severe category for all features, with one exception at the two-year follow-up. All of these abnormalities were significantly associated with time to ROA over 10 years of follow-up.

Table 1. Baseline MRI-Detected Structural Abnormalities and Incident Radiographic Osteoarthritis									
MRI-detected abnormalities at baseline	Knees	Estimated Probability of Radiographic OA			P value*	Hazard Ratio	(95% CI)		
		Within 2 years	Within 4 years	Within 10 years					
Effusion-synovitis									
Physiologic amount	692	0.06	0.10	0.27	<.0001	1.00	ref		
Small	146	0.15	0.31	0.46		2.11	(1.81, 2.42)		
Medium/Large	24	0.48	0.62	0.67		5.10	(3.55, 7.34)		
Hoffa-synovitis									
Normal	593	0.05	0.11	0.25	<.0001	1.00	ref		
Mild	248	0.16	0.24	0.44		1.97	(1.72, 2.26)		
Moderate/Severe	21	0.43	0.43	0.54		4.09	(2.75, 6.07)		
BML, Medial Max Score									
0: none	733	0.08	0.13	0.27	<.0001	1.00	ref		
1: <33%	110	0.12	0.19	0.49		1.82	(1.54, 2.15)		
2/3: >=33%	19	0.39	0.57	0.59		3.82	(2.49, 5.86)		
BML, Whole Knee Max Score									
0: none	339	0.06	0.10	0.21	<.0001	1.00	ref		
1: <33%	333	0.08	0.13	0.33		1.43	(1.22, 1.67)		
2: 33-66%	143	0.14	0.25	0.43		2.14	(1.76, 2.57)		
3: >66%	47	0.34	0.41	0.56		3.25	(2.49, 4.24)		
Cartilage Damage, Surface Area, Medial Max Score									
0: none	558	0.09	0.12	0.21	<.0001	1.00	ref		
1: <10%	146	0.05	0.12	0.36		1.63	(1.38, 1.94)		
2: 10-75%	158	0.19	0.28	0.56		2.85	(2.45, 3.32)		
Cartilage Damage, Full Thickness, Medial Max Score									
0: none	824	0.09	0.15	0.30	<.0001	1.00	ref		
1/2: Any	48	0.18	0.35	0.57		2.70	(2.17, 3.36)		
Cartilage Damage, Surface Area, Whole Knee Max Score									
0: none	146	0.04	0.06	0.13	<.0001	1.00	ref		
1: <10%	235	0.03	0.06	0.18		1.41	(1.05, 1.90)		
2: 10-75%	454	0.13	0.21	0.43		3.67	(2.81, 4.80)		
3: >75%	27	0.43	0.43	0.66		8.66	(3.40, 13.86)		
Cartilage Damage, Full Thickness, Whole Knee Max Score									
0: none	574	0.07	0.11	0.25	<.0001	1.00	ref		
1: <10%	167	0.11	0.20	0.39		1.73	(1.47, 2.02)		
2/3: >10%	121	0.18	0.28	0.52		2.41	(2.04, 2.90)		
Meniscus Extrusion, Medial									
<2 mm	677	0.06	0.12	0.24	<.0001	1.00	ref		
2: 2-3 mm	141	0.19	0.32	0.55		2.51	(2.15, 2.92)		
2/3: >3 mm	44	0.20	0.25	0.55		2.88	(2.27, 3.66)		

*Asymptotic Logrank k-sample test (permutation form), Sun's scores

Conclusion: Our results demonstrate the prognostic value of effusion-synovitis, Hoffa-synovitis, bone marrow lesions, cartilage damage, and meniscal extrusion

for the development of ROA up to 10 years later. Future directions include developing a predictive model that incorporates multiple features.

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Different pathophysiological pathways in axial and peripheral disease: Peripheral and axial spondyloarthritis: to split or to lump?

OP0199

THE HUMAN ENTHESES HARBOURS RESIDENT ADAPTIVE CD4+ AND CD8+ T-CELLS WITH INDUCIBLE IL-17A AND TNF PROTEIN THAT IS PHARMACOLOGICALLY SUPPRESSED BY ROR γ T AND PDE4 INHIBITORS BUT NOT METHOTREXATE IN A NOVEL IN VITRO ENTHESTITIS MODEL

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Background: Animal models have demonstrated that enthesitis is the primary lesion in experimental spondyloarthritis (SpA). In mice, innate lymphocytes were suggested as the major cytokine producers at the enthesis.

Objectives: We tested the hypothesis that the human entheses harbours tissue resident conventional T-cells. We also assessed their ability to express SpA-related cytokines including TNF and IL-17A and if this could be blocked using psoriasis therapeutic agents (methotrexate (MTX), and phosphodiesterase type 4 inhibitor (PDE4i)) and experimental ROR γ T inhibitors (ROR γ Ti).

Methods: Enthesal spinous process was obtained from patients undergoing elective orthopedic procedures (n=20) and mechanically digested or processed for confocal staining and flow cytometry. CD4+ and CD8+ T-cells were sorted and RNA was isolated and analysed by qPCR. Magnetically isolated cells were stimulated using an anti-CD3/CD2/CD28 bead with and without the presence of MTX, ROR γ Ti and PDE4i. Following stimulation IL-17A and TNF were measured by ELISA and intracellular flow cytometry.

Results: CD4+ and CD8+ T-cells represent 35.7% and 23.7% of T-cells in the entheses, respectively, with topographic confirmation by anti-CD3 immunofluorescence staining. Enthesal tissue contained a higher proportion of CD4+ and CD8+ T-cells expressing a resident memory phenotype (CD69+/CD45RA-) compared to matched blood. Sorted T-cells from enthesal tissue had a gene expression profile consistent with a tissue resident phenotype and CD4+ and CD8+ T-cells showed increased expression immunomodulatory genes including IL-10 and TGF- β compared to peripheral blood T-cells (p<0.001). Following stimulation CD4+ T-cells produced more TNF than CD8+ T-cells (p<0.05), IL-17A was robustly detected in CD4+ but not CD8+ T-cells. TNF and IL-17A production from CD4+ T-cells was effectively inhibited by PDE4i (p<0.05), while ROR γ Ti only reduced IL-17 secretion (p<0.001). MTX had no significant impact on both TNF and IL-17A production in either cell population. This pattern of inhibition was mirrored in TNF secretion from CD8+ T-cells.

Conclusion: This is the first description of conventional CD4+ and CD8+ entheses resident T-cells. PDE4i was effective in abrogating induced TNF production and IL-17, whereas ROR γ Ti is highly effective for IL-17A production but not TNF. In contrast, MTX had little effect on *in vitro* enthesitis model cytokine production. These findings may have some practical implications in the treatment of subclinical enthesitis.

Figure 1. Effect of different therapeutic agents on the TNF and IL-17A production by resident enthesal T-cells and matched peripheral blood

Figure 2. Gene expression profile of enthesal T-cells (soft tissue and adjacent bone) compared to peripheral blood

Abbreviations: ST, enthesal soft tissue; PEB, peri-enthesal bone.

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OP0200

A SET OF INFLAMMATORY MARKERS ALLOWING TO DETECT SYSTEMIC INFLAMMATION IN PSORIATIC SKIN, ENTHESEAL AND JOINT DISEASE IN THE ABSENCE OF CRP AND THEIR LINK TO CLINICAL DISEASE MANIFESTATION

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Background: Psoriatic disease is composed of skin, enthesal and joint disease, which can manifest isolated or combined. Little is known about the systemic inflammation levels in psoriatic disease as a robust IL-6 signal is missing and therefore acute phase reactants such as C-reactive protein are often normal. Measuring systemic inflammation in the different manifestations of psoriatic disease is therefore a continuous unmet need.

Objectives: To better define systemic inflammation in patients with psoriatic disease limited to the skin (S), the entheses (E) or the joints (arthritis, A) or with a combination of these disease manifestations (SE, SA, EA, SEA).