12th International Workshop for Osteoarthritis Imaging

Structure and symptoms: are the Big Two coming together with the help of imaging?

Chair: Ali Guermazi

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July 5-8, 2018 Menton, France

Welcome to the 12th International Workshop on Osteoarthritis Imaging

The International Workshop on Osteoarthritis Imaging started in 2007 and was held in Ainring, Germany, with 126 registered participants from academia, regulatory and funding agencies, and industry. Since then, the Workshop has been held annually at various locations around the globe.

This workshop is a unique opportunity for scientists, researchers, regulatory agencies, interested members of pharmaceutical companies and others to meet and have an in depth and open minded discussion about the best way to advance the field of osteoarthritis imaging.

For years, we have been trying to understand osteoarthritis from the imaging point of view. We now have a large amount of imaging and clinical data available on osteoarthritis and it is an optimal time to move forward and expand on our understanding of the disease.

What's happening in 2018?

- This year we are so excited to present a program more engaged than previous workshops where we are calling this conference the ultimate engagement and intersection of academia and industry.

- As in previous workshops, there will be an emphasis on emerging techniques, but also translation to clinical practice and trials beyond imaging. There will be ample opportunity and time specifically allotted for discussion (more than in previous years) and specific interaction between industry and academia.

Sincerely,

Ali Guermazi, M.D., Ph.D.
Chairman
International Workshop on Osteoarthritis Imaging
Professor of Radiology & Medicine
Boston University School of Medicine

An Olympic Thank You to Our 2018 IWOAI Sponsors!!

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Day 1 (Thursday July 5)

09:00-17:00 Registration desk open

Pre-Course Workshop: Hands on musculoskeletal ultrasound with live demonstration
Moderators: Michel Crema, Lionel Pesquer, Simo Saarakkala, Jean-Louis Brasseur
Support from Hitachi France

09:00-10:15 Pre-course Workshop part 1: Ultrasound of knee and shoulder

10:15-10:30 Coffee break

10:30-11:45 Pre-course Workshop part 2: Ultrasound of hand and hip

12:00-13:30 Lunch at Royal Westminster Hotel

13:30-14:00 Welcome and Introduction - Ali Guermazi - Chair

14:00-15:30 Session 1: DMOAD Development and Biomarker Qualification
Moderator: Kent Kwoh

14:00-14:20 Novel analytic and computational approaches – is big data the solution?
Elena Losina

14:20-14:40 The case of wet biomarkers in DMOAD trials – Complementary, better or worse than imaging?
Ali Mobasheri

14:40-15:00 Where are we on the road to qualification of MRI for drug approval?
Kent Kwoh

15:00-15:20 Do we need more than X-ray for eligibility evaluation?
Frank Roemer

15:20-16:00 Discussion

16:00-16:30 Coffee break & Poster viewing

16:30-16:45 Young investigator award presentation – Mikael Boesen & Olga Kubassova

16:45-17:45 Proffered papers
Moderator: Erik Dam

16:45-16:55 Fluorescence optical imaging is associated with joint pain in hand OA
Øystein Maugesten et al.

16:55-17:05 Simultaneous T2 mapping and morphological imaging of the osteoarthritic knee using a rapid 5 minutes DESS MRI scan
Susanne Eijgenraam et al.

17:05-17:15 Skin temperature of the patella increases with osteoarthritic severity
Jerome Thevenot et al.

17:15-17:25 Superficial and deep cartilage T2 is not predictive but increases concurrently with fast progression in early radiographic knee OA (KLG1) – Data from the OAI
Wolfgang Wirth et al.

17:25-17:35 Delayed gadolinium enhanced MRI of menisci and cartilage (dGEMRIM/dGEMRIC) in obese patients with knee OA: Cross-sectional study of 85 obese patients with intra-articular administered gadolinium contrast
Stine Hangaard et al.

17:35-17:45 Analysis of dual energy CT (DECT) scans to detect signs of osteoarthritis associated urate in articular cartilage or meniscus of the knee
John Lynch et al.

19:00 Dinner at Paris Palace, Menton

Day 2: (Friday July 6)

09:00-17:00 Registration desk open

09:00-10:30 Session 2: Where we are with the technology? Oldies we know!
Moderator: Jeff Duryea

9:00-9:20 Semi-quantitative analysis of BML, cartilage and inflammation as imaging biomarkers
Michel Crema

9:20-9:40 Compositional MRI cartilage and beyond. Any role in DMOAD development?
Richard Kijowski

9:40-10:00 3D quantitation: will it the first FDA accepted imaging endpoint?
Felix Eckstein

10:00-10:30 Discussion

10:30-11:00 Coffee Break & Poster viewing

11:00-12:30 Session 3: Where we are with the technology? New techniques to know!
Moderator: Shadpour Demehri

11:00-11:20 Role of extremity CT imaging in OA (technical, clinical, research)
John Carrino

11:20-11:40 What is truly novel and has a potential? Upcoming developments in imaging technology potentially applicable to DMOAD trials
Edwin Oei

11:40-12:00 Bone shape, deep leaning and pattern recognition. Imaging and Beyond
Mike Bowes

12:00-12:30 Discussion

12:30-14:00 Lunch at Royal Westminster Hotel

14:00-16:00 Session 4: Randomized controlled trials, large datasets and more
Moderator: Peter Steiger

14:00-14:20 Why is it so challenging to perform randomized controlled trials beyond the

uniform agreement that we need “better data” in order to move on
Jos Runhaar

14:20-14:40 The APPROACH project – what is novel and where do we stand
Chris Ladel

14:40-15:00 Is there a role for ultrasound in OA clinical trials?
Simo Saarakkala

15:00-15:30 Discussion

15:30-16:00 Coffee Break and Poster viewing

16:00-17:30 Proffered papers
Moderator: Wolfgang Wirth

16:00-16:10 A naturally ageing knee, or development or early knee osteoarthritis? Data from the osteoarthritis initiative
Karin Magnusson et al.

16:10-16:20 Fully-automated 2D magnetic resonance thigh muscle image segmentation using a deep learning technique
Jana Kemnitz et al.

16:20-16:30 Fully-automated segmentation of knee joint anatomy using deep convolutional neural network approach
Richard Kijowski et al.

16:30-16:40 Knee segmentation by multiplanar deep learning network – With data from the OAI
Mathias Perslev et al.

16:40-16:50 High patient throughput 5-minute comprehensive quantitative bilateral knee MRI
Feliks Kogan et al.

16:50-17:00 Three-dimensional MRI for the depiction of knee meniscal injuries: A metaanalysis diagnostic performance
Delaram Shakoor et al. (Second Best Abstract Award)

17:00-17:10 Mechanical stress around cysts is related to knee pain in patients with knee osteoarthritis: A subject-specific finite element study
James Johnston et al.

17:10-17:20 Open-sourced deep-learning for cartilage cartilage and meniscus segmentation
Akshay Chaudhari et al. (First Best Abstract Award)

17:20-17:30 Application of deep learning for the quantitative assessment of bone marrow lesions
Frank Preiswerk et al. (Second Best Abstract Award)

19:00 Dinner at Café de Paris, Monaco

Day 3: (Saturday July 7)

08:00-12:00 Registration desk open

09:00-10:30 Session 5: Pain treatment in OA patients – Clinical
Moderator: Marc Hochberg

9:00-9:20 A primer on pain and OA – What have we learned from imaging in the last 5 years?
Philip Conaghan

9:20-9:40 How important is central sensitization and does imaging play a role?
Tuhina Neogi

9:40-10:00 Are we wasting time and money pursuing the search for the Holy Grail? – Analgesic therapy vs. disease modification
Marc Hochberg

10:00-10:30 Discussion

10:30-11:00 Coffee Break and Poster viewing

11:00-12:30 Session 6: Pain treatment in OA patients – Imaging
Moderator: Colin Miller

11:00-11:20 Challenges and potential solutions in multicenter anti-NGF studies – the CRO perspective
Souhil Zaim

11:20-11:40 The tanezumab program – Update on its current status
Mark Brown

11:40-12:00 Why imaging has become important in anti-NGF trials and why every OA patient

is structurally different?
Ali Guermazi

12:00-12:30 Discussion

12:30-14:00 Lunch at Royal Westminster Hotel

14:00-15:30 Session 7: Publishing in OA
Moderator: Ali Mobasheri

14:00-14:20 The need for publication of negative studies in order to advance the field
Tonia Vincent

14:20-14:40 Has publication of OA imaging studies become more challenging in last years?
Joel Block

14:40-15:00 Is there room and need for an OA imaging journal? Name and format?
Ali Guermazi & All attendees

15:00-16:00 Proffered papers
Moderator: John Carrino

15:00-15:10 Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: Two-year clinical, structural, and biomarkers outcomes
Mylène Jansen et al.

15:10-15:20 The relationship between imaging biomarkers and knee replacement is as strong as that for patient reported outcomes (PROS) of knee pain symptoms
Felix Eckstein et al.

15:20-15:30 Short-term structural progression on MRI is related to incident radiographic and clinical knee OA, but is it relevant for prediction?
Jos Runhaar et al.

15:30-15:40 Intra-articular Sprifermin in symptomatic radiographic knee osteoarthritis: A post-hoc multi-tissue analysis of MRI-defined change of the 2-year data from a 5-year randomized, placebo-controlled, phase II study
Frank Roemer et al.

15:40-15:50 Communicating clinical relevance of an imaging biomarker with probability: Predicting knee replacement with total cartilage thickness
Kent Kwoh et al.

15:50-16:00 Association between gout and MRI-based knee osteoarthritis worsening:

Preliminary analysis from the FNIH study
Arya Haj-Mirzaian et al.

16:00-16:30 Coffee Break and Poster viewing

16:30-17:30 Session 8: Panel discussion involving pharmaceutical representatives: Do we need more (data) or do we need to understand (existing) data better in order to move on?
Christopher Ladel
Kent Kwoh
Marc Hochberg
Jeffrey Kraines

17:30-17:45 Promotion of the next year's workshop
James (J.D.) Johnston & Emily McWalter

19:30 Gala Dinner at Palais de l'Europe, Menton

Day 4: (Sunday July 8)

09:00 Post Workshop trip and socializing: visit 2 medial villages in Italy

SCIENTIFIC TALKS

FLUORESCENCE OPTICAL IMAGING IS ASSOCIATED WITH JOINT PAIN IN HAND OA

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**Department of Rheumatology and Clinical Immunology, Charité Universitätsmedizin, Berlin, Germany

INTRODUCTION:Previous hand OA studies have demonstrated an association between pain and synovitis detected by MRI and ultrasound. No studies have explored the validity of fluorescence optical imaging (FOI), an imaging technique showing altered microcirculation in hand joints, as a sign of inflammation.

OBJECTIVE: 1) To quantify the distribution of FOI findings in different joint groups in hand OA patients, and 2) explore associations between FOI findings and pain through clinical examination and by self-report.

METHODS: In the Norhand study, 249 patients (88% female, median age (IQR) 61 (56-66) years) underwent FOI of both hands, bilateral clinical joint examination for tenderness on palpation and movement, and self-reported pain in individual joints on the homunculus. The FOI scan was performed after the administration of an intravenous fluorescence dye (indocyanine green, ICG), and 360 images (1/second) were produced. Based on the inflow and washing out of the dye, the pictures were divided into 3 phases. Finally, the prima vista mode (PVM) represented a composite picture of the first 240 images. For each phase fluorescence enhancement in the joints was graded from 0 to 3 based on signal intensity. To study the association between FOI findings and pain in the same joint, we applied logistic regression analysis with generalized estimating equations adjusting for age, sex, and BMI. Separate models were applied for each of the FOI phases and pain outcomes.

RESULTS: The median (IQR) number of distal (DIP) and proximal interphalangeal (PIP) joints with FOI enhancement within each patient ranged from 0 (0-0) in phase 1, 14 (11-16) in phase 2, 3 (0 - 8) in phase 3, and 9 (7-11) in PVM. Regardless of the phase, the 1st carpometacarpal (CMC-1) and metacarpophalangeal joints showed no and uncommon enhancement respectively, and the associations between FOI and pain were therefore analysed in the DIP and PIP joints only. FOI enhancement in the DIP and PIP joints was associated with pain in the same joint consistent for all three pain outcomes (table). A dose-response relationship was found for phase 2, phase 3, and PVM, but not in phase 1.

Associations between FOI Enhancement and Pain in the same DIP and PIP Joints

		Joint pain last 24h OR (95 % CI)	Joint pain last 6 weeks OR (95 % CI)	Joint tenderness OR (95 % CI)
FOI Phase 1	Grade 0	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	Grade 1-3*	1.76 (1.04, 2.96)	2.01 (1.23, 3.25)	2.36 (1.32, 4.21)
FOI Phase 2	Grade 0	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	Grade 1	1.26 (1.00, 1.58)	1.30 (1.03, 1.64)	1.22 (1.01, 1.48)
	Grade 2	1.88 (1.47, 2.41)	2.05 (1.59, 2.60)	1.49 (1.22, 1.83)
	Grade 3	2.15 (1.50, 3.07)	2.74 (1.91, 3.93)	2.15 (1.58, 2.94)
FOI Phase 3	Grade 0	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	Grade 1	1.38 (1.10, 1.73)	1.41 (1.13, 1.75)	1.34 (1.12, 1.61)
	Grade 2+3*	1.90 (1.08, 3.34)	2.23 (1.32, 3.78)	1.93 (1.22, 3.05)
FOI PVM	Grade 0	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	Grade 1	1.23 (1.03, 1.48)	1.41 (1.17, 1.70)	1.27 (1.09, 1.49)
	Grade 2**	2.11 (1.64, 2.70)	2.26 (1.77, 2.89)	1.90 (1.54, 2.34)

*Combined grades due to few joints with enhancement **No joints with grade 3 in PVM

CONCLUSION: Hand OA patients had frequent FOI enhancement in the DIP and PIP joints, whereas the method seems insensitive to detect inflammation in CMC-1. FOI enhancement was related to pain and tenderness in the same joint, supporting the validity of the FOI examination in patients with hand OA.

SPONSOR: None.
DISCLOSURE STATEMENT: None.
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SIMULTANEOUS T_2 MAPPING AND MORPHOLOGICAL IMAGING OF THE OSTEOARTHRITIC KNEE USING A RAPID 5 MINUTES DESS MRI SCAN

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INTRODUCTION: Quantitative MRI measures such as T_2 mapping, and semi-quantitative assessments such as MRI Osteoarthritis Knee Score (MOAKS), are commonly used to track spatial and temporal changes of knee OA. Acquiring these biomarkers currently requires multiple lengthy MR sequences, resulting in long MRI protocols. Recent research has shown that the Dual Echo Steady State (DESS) MRI sequence can be used to acquire a combination of detailed morphological images for MOAKS scoring and accurate T_2 measurements in various knee tissues with only 5minutes scan time. While promising, an evaluation of DESS in OA subjects is important to determine its feasibility in clinical studies of OA.

OBJECTIVE: To investigate consistency of quantitative and semi-quantitative MR imaging biomarkers of knee OA, obtained with a 5-minute DESS sequence, in patients with increasing stages of OA.

METHODS: DESS generates two echoes per repetition time; one echo with T_1/T_2 contrast, which (resembling proton-density (PD) contrast), and one echo with T_2 weighting. Unlike traditional uses of DESS, the DESS sequence used in this study generates two separate echoes. The high SNR-efficiency of DESS can be used to generate axial and coronal reconstructions with diagnostic image quality for both echoes. In this study, 54 patients were included and divided into three groups, based on their radiographic degree of knee OA (Kellgren and Lawrence): 20 patients with no knee OA (KLG 0), 18 patients with mild knee OA (KLG 2) and 16 patients with moderate knee OA (KLG 3). All patients were scanned using DESS. MOAKS was performed by a researcher experienced in musculoskeletal MRI. Mean T_2 values of cartilage (femur and tibia, medial and lateral) and meniscus (medial and lateral) were calculated on single slices, using in-house developed post-processing software. Statistical testing between KL-groups was performed with one-way ANOVA tests, using an alpha of 0.05 as significance threshold. Correlation between T_2 values and MOAKS was assessed using a linear regression model.

RESULTS: T_2 values of cartilage and menisci, as well as MOAKS subscores are shown in Table 1. The differences in T_2 values and MOAKS subscores between the three groups were statistically significant for both cartilage and meniscus ($p < 0.001$). Mean T_2 values of cartilage showed a moderate-to-strong correlation with corresponding MOAKS cartilage findings ($r = 0.61$, $p = 0.002$).

	T_2 Femoral Cartilage ± SD (ms)	T_2 Tibia Cartilage ± SD (ms)	T_2 Medial Meniscus ± SD (ms)	T_2 Lateral Meniscus ± SD (ms)	MOAKS Subscore Cartilage ± SD (Thinning, full-thickness defects)	MOAKS Subsco Meniscus ± SD (Signal, tears, maceration)
No OA	36.9 ± 4.7	35.2 ± 3.8	15.7 ± 4.1	15.1 ± 2.5	0.9 ± 1.7	2.3 ± 3.9
Mild OA	41.6 ± 5.6	39.2 ± 6.2	18.4 ± 3.2	17.7 ± 3.3	7 ± 6	5.3 ± 3.9
Moderate OA	48.6 ± 7.8	43.9 ± 8.2	20.7 ± 6.1	21.3 ± 6.7	14.8 ± 7.8	6.8 ± 4.1

CONCLUSIONS: Simultaneous quantitative T_2 and semi-quantitative assessment of cartilage and meniscus with a 5-minute DESS-sequence show consistent outcomes with increasing stages of degeneration, making this sequence a useful tool for OA research.

SPONSOR: Osteoarthritis Research Society International (OARSI) Young Investigator Collaborative Scholarship 2017
DISCLOSURE STATEMENT: None
ACKNOWLEDGMENT: None
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SKIN TEMPERATURE OF THE PATELLA INCREASES WITH OSTEOARTHRITIC SEVERITY

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INTRODUCTION: Multiple studies have demonstrated that thermal imaging can assess inflammatory process of tissues occurring in disorders such as OA. Despite promising results, there is a lack of standardized protocol to acquire the relevant information in the studied joints, which would allow comparisons among different studies.

OBJECTIVE: The aim of this study was to establish a protocol of thermal imaging acquisition and analysis to assess the performance of this modality in the evaluation of osteoarthritic severity of the knee joint.

METHODS: A total of 66 females (age 57.8±6.2) were recruited for a clinical trial and their right knee underwent a radiological examination. Kellgren-Lawrence grading (KLG) was assessed from plain radiography and MOAKS grading from MRI imaging. Furthermore, thermal images were acquired from frontal, lateral and medial views of the studied legs. A custom-made algorithm was developed in Matlab to manually segment different local regions of interest (ROIs) from the thermal images. For each ROI, the average temperature was calculated and divided by the overall cutaneous temperature of the whole leg assessed from both the medial and lateral views, to normalize the thermal information among the subjects. These temperature ratios were then compared to the KLG and both the Hoffa-synovitis and effusion-synovitis scores using Pearson correlations. ROC analyses were also applied to assess the performance of the method to discriminate OA patients (KLG ≥ 2) from controls, and to detect the presence of synovitis (Hoffa ≥ 1 and effusion score ≥ 1).

RESULTS: Within all the ROIs assessed in the joint area, the ROI located on top of the patella provided the most statistically significant results. The ratio patella / mean leg temperatures increased with KLG (R=0.53, p<0.001), Hoffa (R=0.63, p<0.001) and effusion-synovitis (R=0.46, p<0.001) scores, with the ability to detect synovitis >70% (Table 1).

CONCLUSION: Basic thermal analysis can already provide some hints on knee OA severity and can detect MRI findings related to synovitis. With OA, the cutaneous temperature of the patella increases (Figure 1) while it remains lower in healthy subjects. This approach offers an alternative low-cost option to get further information in OA diagnostics.

Table 1. Correlations between patella / mean leg temperature ratio and radiological findings (N=66).

	KLG	Hoffa-synovitis	Effusion - synovitis
Pearson correlation	0.53***	0.63***	0.46***
Condition (positives / negatives)	KLG ≥ 2 (34 / 32)	Hoffa ≥ 1 (40 / 26)	Score ≥ 1 (37 / 29)
Area under the curve (ROC)	0.77	0.81	0.70

***p<0.001, ROC receiving operator characteristic.

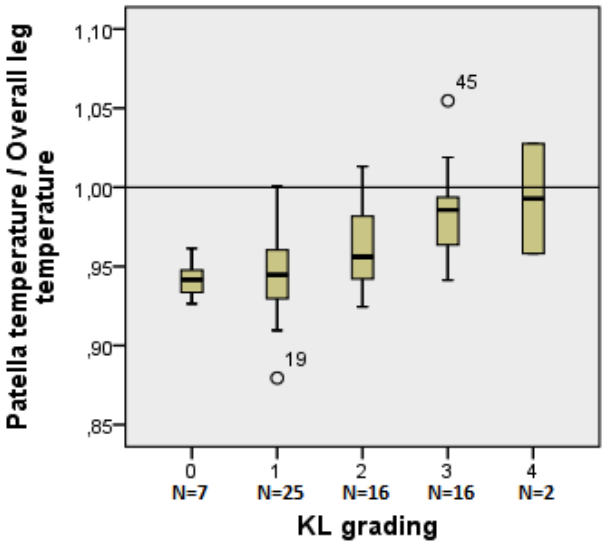

Figure 1. Distribution of the temperature ratios with KLG (N=66).

SPONSOR: Infotech Oulu and Business Finland.
DICLOSURE STATEMENT: none.
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SUPERFICIAL AND DEEP CARTILAGE T2 IS NOT PREDICTIVE BUT INCREASES CONCURRENTLY WITH FAST PROGRESSION IN EARLY RADIOGRAPHIC KNEE OA (KLG1) – DATA FROM THE OAI

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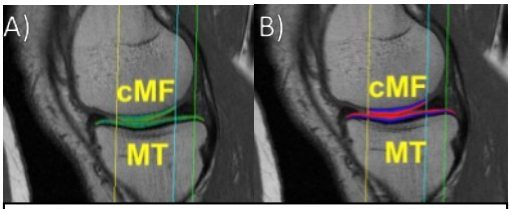
INTRODUCTION: Cartilage transverse relaxation time (T2) is considered to represent cartilage composition, and to be sensitive to early OA-related change. Liebl et al. reported that cartilage T2 was elevated in knees progressing from KLG0 to KLG ≥2 over 4 years and suggested cartilage T2 to predict the subsequent onset of radiographic OA [1]. T2 may thus be a useful imaging biomarker in the design of clinical studies that test disease-modifying drugs (DMOADS) at an early stage of knee OA, as it may help identifying participants with fast structural progression. In the current work, we analyzed laminar (superficial and deep layer) cartilage T2 in knees with early baseline radiographic OA (KLG1) that developed advanced radiographic disease (i.e., KLG ≥ 3 with OARSI JSN grade 2 or 3) over the next 4 years (case knees), a process accompanied by substantial rates of cartilage thickness loss [2]. These case knees were compared with matched control knees that maintained KLG1 status throughout the observation period and showed only moderate changes in cartilage thickness [2].

OBJECTIVE: To determine 1) whether baseline (superficial or deep) cartilage T2 differs between case and control knees, and 2) whether 1- and 4-year longitudinal change in T2 differs between case and control knees.



Cartilage T2 analysis (MT=medial tibia, cMF =central medial femur).A) Color-coded T2; B) Superficial (red) / deep (blue) cartilage layer.

METHODS: In the OAI, 76 KLG1 knees from 76 OAI participants developed KLG 3 or 4 (OARSI JSN grade 2 / 3) between baseline and year-4 follow-up (case knees), whereas 995 KLG1 knees maintained KLG1 status over this period (control knees). 3T multi-echo spin-echo (MESE) MRIs were only acquired in right knees by the OAI, therefore only 39 right case knees (67% women; age 62.5±7.6 y, BMI: 30.3±4.4) could be matched 1:1 to 39 right control knees (age ±5y; BMI ±5, WOMAC pain ±5; same OARSI JSN grade and sex). Cartilage T2 at baseline (BL), year-1, and year-4 follow-up (Y1/Y4 FU) was calculated for the superficial and deep cartilage layer (each 50% of cartilage thickness) in the medial and lateral femorotibial compartment (MFTC/LFTC), based on manual, quality-controlled cartilage segmentations of the MESE MRIs (with year-4 MRIs available for 37 of 39 matched pairs).

RESULTS: Baseline cartilage T2 did not differ statistically significantly between case and control knees in either the superficial or deep layer of the MFTC or LFTC (MFTC superficial: 49.9±4.5 ms vs. 51.1±5.5 ms, p=0.24 [paired t-test]; deep: 38.0±2.5 ms vs. 38.5±3.2 ms, p=0.54; LFTC: superficial: 47.1±2.6 ms vs. 48.0±2.9 ms, p=0.14; deep: 36.8±1.9 ms vs. 36.8±2.2 ms, p=0.97). Longitudinal change in cartilage T2 differed statistically significantly between case and control knees in the MFTC (BL→Y1 FU: superficial: 0.8±3.4 ms vs. -0.8±3.6 ms, p=0.04; deep: 0.9±3.1 ms vs. -0.1±1.8 ms, p=0.03; BL→Y4 FU: superficial: 4.2±7.6 ms vs. 0.8±2.6 ms, p=0.01; deep: 4.3±8.4 ms vs. 0.8±2.1 ms, p=0.02) but not in the LFTC (data not shown).

CONCLUSION: Baseline cartilage T2 was not found to be associated with subsequent radiographic progression from KLG1 to KLG ≥3 over 4 years. However, structural progression appeared to be accompanied by a concurrent increase in cartilage T2 in both the MFTC superficial and deep cartilage layers. The results of this study thus do not lend support to cartilage T2 as a biomarker that predicts structural progression, but T2 rather seems to change concurrently with cartilage thickness loss.

REFERENCES: [1] Liebl et al. 2015 Ann Rheum Dis; [2] Maschek et al.: same conference

SPONSOR: Merck KGaA, Darmstadt, Germany
ACKNOWLEDGMENT: The OAI participants and investigators, the Chondrometrics readers
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DELAYED GADOLINIUM ENHANCED MRI OF MENISCI AND CARTILAGE (dGEMRIM/dGEMRIC) IN OBESE PATIENTS WITH KNEE OA: CROSS-SECTIONAL STUDY OF 85 OBESE PATIENTS WITH INTRA-ARTICULAR ADMINISTERED GADOLINIUM CONTRAST

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******Department of orthopedics, Clinical Sciences Lund, Lund University, Skåne University Hospital, Lund, Sweden

BACKGROUND Morphologic degenerative changes in the menisci are highly associated with development of knee osteoarthritis (OA). Early cartilage changes in knee OA can be assessed by both intravenous (i.v.) and intra-articular (i.a.) delayed Gadolinium enhanced MRI of cartilage (dGEMRIC) and preliminary results have shown that an i.v. dGEMRIC approach might be able to quantify the degeneration in menisci called delayed Gadolinium enhanced MRI of Menisci (dGEMRIM).

OBJECTIVE: The aim of this study was first to examine the relationship between i.a. dGEMRIC and dGEMRIM in overweight patients with knee OA and secondly to investigate if the same i.a. dGEMRIC approach can be used to assess the morphological degeneration of menisci by means of dGEMRIM.

METHODS: 85 obese patients (BMI>30) with knee OA from the CAROT-study (Clin trial id: NCT00655941) with a median Kellgren and Lawrence grade (KLG) of 3 were included. Meniscus morphology was assessed according to MRI osteoarthritis knee score (MOAKS) as increased signal/no signal (1/0) and tear/no tear (1/0) in the posterior meniscal horn on sagittal proton density weighted MRI images. The signal- and tear scores were summed to obtain a total score ranging 0-2. For dGEMRIC and dGEMRIM all patients had an ultrasound guided i.a. injection of negatively charged Gadolinium (Multihance). T1-relaxation time mapping was performed on a 1.5T Philips scanner (Intera) with a time delay of 90-120 minutes after injection using an inversion recovery sequence with four inversion times (50, 350, 650, 1410 ms). T1-relaxation time dGEMRIC values were calculated for posterior weight bearing femoral cartilage in the lateral knee compartment, and the posterior meniscal horns of both lateral and medial menisci were used for dGEMRIM. Due to advanced medial knee OA and thus missing cartilage in the weight bearing part of the femur and tibia in the majority of patients, dGEMRIC in the medial compartment could not be performed and measured.

RESULTS: For lateral menisci, morphology sum scores of 0, 1 and 2 were found in 13, 58 and 14 patients, respectively and for medial menisci in 2, 30 and 30 patients, respectively. Mean T1-relaxation time was 441 ms (range 301-571 ms) in posterior femoral cartilage (N=85); 497 ms (range 291-693 ms) in the lateral menisci (N=84) and 480 ms (range 263-699ms) in the medial menisci (N=62). T1-relaxation times for the medial and lateral menisci were similar (p=0.53), and a weak correlation was found between dGEMRIC and dGEMRIM in the lateral knee compartments (R= 0.26). Comparing dGEMRIM in patients with different morphology sum scores (0-2) showed no significant difference (p>0.4).

CONCLUSION: No correlation was found between the degree of meniscal degeneration and meniscus T1-relaxation times. I.a. dGEMRIM does not seem to be applicable in this large group of OA patients - supporting the hypothesis that GAG-depletion is not part of the meniscal degeneration in the same manner as cartilage. The correlation between i.a. dGEMRIC and dGEMRIM and the similar dGEMRIM values in the medial and lateral menisci supports the assumption of knee OA as a whole joint degenerative disease indicating that i.a. dGEMRIC may still be an alternative contrast saving methods to consider taking the recent regulatory warnings regarding the use of i.v. Gadolinium in mind.

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ANALYSIS OF DUAL ENERGY CT (DECT) SCANS TO DETECT SIGNS OF OSTEOARTHRITIS ASSSOCIATED URATE IN ARTICULAR CARTILAGE OR MENISCUS OF THE KNEE

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INTRODUCTION: Mineralization of articular cartilage or meniscus frequently seen in knee osteoarthritis (OA) and is considered to be solely related to calcium-based crystals. While urate in serum and synovial fluid have been associated with OA, little is known about whether such mineralization in knee OA is ever mainly from urate.

OBJECTIVE: Develop a method to detect urate in the cartilage or meniscus from DECT of the knee.

METHODS: DECT knee scans of participants from the Multicenter Osteoarthritis Study are being scored by a radiologist (MJ) for the presence/absence/location and severity of mineralization in cartilage and meniscus. The National Institute of Standards and Technology (NIST) Physical Measurement Laboratory XCOM database (https://physics.nist.gov/PhysRefData/Xcom/html/xcom1.html) was used to estimate x-ray attenuation properties of water, uric acid and calcium hydroxyapatite across the diagnostic range of x-ray photon energies (40-150 keV) and the results used to develop a method to determine whether mineralized cartilage or meniscal tissue could contain urate.

RESULTS: Soft tissue containing urate was shown to have a relatively constant HU value, varying by about 5% across the diagnostic x-ray photon energy range (40-150 keV). Therefore any voxels in a knee DECT scan containing urate crystals would have elevated HU but similar values on both high and low energy CT scans. Calcium based mineralization was shown to have much greater HU variation and the ratio of low energy HU to high energy HU values would be about 1.9 on the Siemens SOMATOM Force using protocol for this study. Axial CT slices close to the tibiofemoral joint were analyzed as a 3D volume, excluding voxels containing air. Two-dimensional joint histograms of (high energy HU, low energy HU) were then calculated, from which the ratio of low energy HU to high energy HU values were calculated. After excluding voxels with HU values less than the mean value for soft tissues (assumed to contain no mineral), a 2D histogram (Fig 1) of # of voxels by (HU ratio, HU value) was calculated for each knee. These showed that calcium hydroxyapatite appeared as voxels with elevated HU with a HU ratio of around 1.9. Fig 1 also shows the location on the histogram in which any voxels from cartilage or meniscus that contained only urate crystals within soft tissue would appear. From the 8 knees analyzed to date, there was been no sign of voxels in which the mineralization of cartilage or meniscus was mainly from urate.

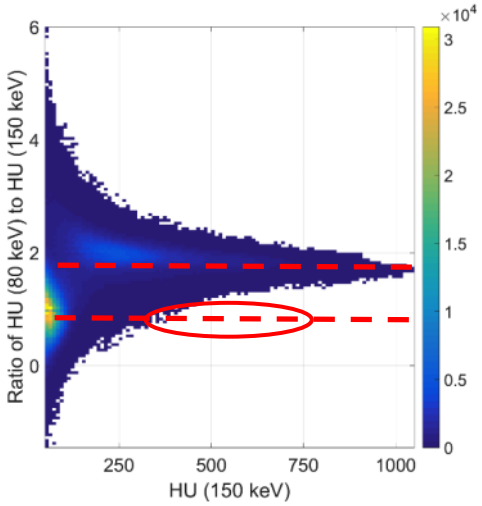

Figure 1. Two dimensional joint histogram of (y-axis) low energy to high energy HU ratio with (x-axis) high energy HU. White represents no voxels, dark blue represents few voxels, light blue more voxels, and green thru yellow represent even more voxels. Urate based voxels would be expected within the red oval lying on y=1.0. Calcium based mineral lies around y=1.9 (upper dashed red line)

CONCLUSIONS: DECT images can be acquired for the same time and radiation dose as single energy CT scans and this has enabled the development of a method that can enhance the ability to determine whether cartilage or meniscus contain any urate based crystals. Further work is required to (a) exclude voxels within or very close the femur or tibia, (b) improve the segmentation of mineralized tissue from soft tissue by using dual energy parameters, and (c) examine the skewness of the HU ratio distribution to examine whether voxels of mixed calcium/urate crystals can be identified.

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ACKNOWLEDGMENT: Staff at the Coordinating Center at UCSF and at the clinical sites in Iowa and Alabama
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A NATURALLY AGEING KNEE, OR DEVELOPMENT OF EARLY KNEE OSTEOARTHRITIS? DATA FROM THE OSTEOARTHRITIS INITIATIVE

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PURPOSE: At IWOAI 2017 we reported on high prevalence of MRI features indicative of early OA in both subjects with and without OA risk factors. The current aim was to determine the further *development* of early knee osteoarthritis (OA) in subjects *with* and *without* risk factors for knee OA.

METHODS: We studied 340 subjects from the Osteoarthritis Initiative, aged 45-55 years (51% women), free of radiographic knee OA at baseline (n=294 *with* and n=46 *without* knee pain and other OA risk factors). At baseline, 24, 48, 72 and 96 months we compared the two groups for prevalence and overlap of knee OA as defined by magnetic resonance imaging (MRI) (MRI-based OA), x-rays (Kellgren-Lawrence grade [KLG]≥1), and knee pain, using a logistic mixed model. We studied the group differences (%) over time by subtracting the OA prevalence of those without risk factors from the group with risk factors.

RESULTS: We observed an increasing prevalence of MRI-based OA from baseline to 72-months for both groups. The group *with* OA risk factors had a higher proportion with MRI-based OA than the group *without* OA risk factors at all visits, but the difference was attenuated at 72 months (72 months difference =11.9%, 95% CI=-2.3-26.1). Further, at the 72-month follow-up, the presence of KLG≥1 were similar in the two groups (-3.5%, 95% CI=-15.2-8.2) (Table). The proportion fulfilling all three OA definitions was 1.7% at 24 months and 4.8% at 72 months of those *with* OA risk factors and 0% and 2.2%, respectively, in those *without*.

TABLE. The differences between the group *with* risk factors and the group *without* risk factors in prevalence of different OA definitions.

	Baseline	24 months	48 months	72 months	96 months
MRI OA (TF)	14.4 (5.0-23.9)	19.4 (9.0-29.8)	20.0 (7.7-32.3)	11.9 (-2.3-26.1)	NA
KLG≥1	NE	2.9 (-2.1-7.9)	-5.0 (-14.8-4.8)	-3.5 (-15.2-8.2)	1.4 (-10.5-13.3)
Knee pain	NE	49.8 (36.8-62.8)	39.2 (24.7-53.7)	44.0 (29.7-58.1)	47.7 (34.0-61.4)

Data are percentage group differences with 95% confidence intervals, representing the group *without* risk factors subtracted from the group *with* risk factors. Abbreviations: NA; no available data, NE; not estimable, TF; tibiofemoral compartment. No MRI data was available at the 96 months follow-up.

DISCUSSION: The current longitudinal study of different operational definitions of OA sheds new light on the complexity of early OA development and what can potentially be considered as 'normal' aging of the knee. Our findings indicate that operational MRI or X-ray definitions of OA in isolation cannot efficiently distinguish between what is natural aging and what is to become clinically relevant-knee OA.

CONCULSIONS: Structural OA development is common irrespective the presence of pain or other OA risk factors, and these structural features should probably be considered as a *risk factor* for OA rather than disease *per se*.

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ACKNOWLEDGMENT: The Osteoarthritis Initiative (OAI)
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FULLY AUTOMATED 2D MAGNETIC RESONANCE THIGH MUSCLE IMAGE SEGMENTATION USING A DEEP LEARNING TECHNIQUE

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INTRODUCTION: Knee OA and other musculoskeletal disorders have a high prevalence among the population and are the most frequent cause for knee pain, functional limitation and loss in quality of life [1]. Thigh muscle status has been reported to be associated with symptoms in knee OA and automated segmentation of thigh muscles is an important step towards investigating the impact of muscle morphology in relation to clinical outcome from large available datasets such as the Osteoarthritis Initiative (OAI).

OBJECTIVE: The recent development in machine learning and parallel computing infrastructure enable segmentation techniques based on deep convolutional neural networks (CNN). We therefore investigated the suitability of 2D state-of-the-art CNNs for the automated segmentation of the cross-sectional areas of the quadriceps, hamstrings, subcutaneous fat (SCF) and the femoral bone from thigh MRIs of the OAI.

METHODS: The segmentation method was implemented in Python 3.4 using a 2D U-Net CNN symmetric up- and down sampling architecture [2]. We used N=1499 axial thigh MRIs acquired at approximately 33% of the thigh (from distal to proximal) using a T1-weighted spine echo sequence, which had been previously segmented using a semi-automated approach [3, 4]. The proposed dataset was randomly divided into a training (N=1449) and validation set (N=50). The MRI images where cropped and centered towards the femoral bone of the right knee, to simplify the segmentation problem with a resulting image size of 256 × 265 pixels for the introduced network architecture. We evaluated the segmentation accuracy using three measures: the Dice similarity coefficient (DSC), the Hausdorff distance (HD), and Bland-Altman plots.

RESULTS: The overall DSC (0.98±0.01), HD (3.83±4.33) and the small intruded bias towards our previous method (≤1%) compare favorably to the related literature [5].

Table 1: Segmentation accuracy obtained by the 2D U-Net vs semi-automated segmentation

	Quadriceps	Hamstrings	Subcutaneous Fat	Femoral Bone
Dice Similarity Coefficient	0.98±0.00	0.98±0.01	0.99±0.01	0.97±0.02
Hausdorff Distance	4.29±2.05	5.85±3.27	3.47±7.10	1.17±0.89

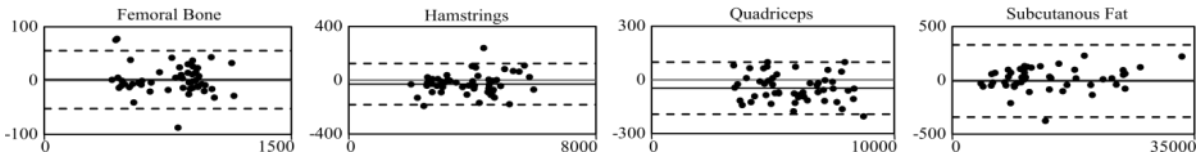

Figure 1: Bland-Altman sowing the introduced segmentation bias vs semi-automated segmentation [≤ 1%]

CONCULSION: The 2D state-of-the-art CNN architecture evaluated in this work enables fully automatic segmentation of anatomical cross-sectional areas of muscle and adipose tissue in the thigh. This novel approach can be applied to fully automated evaluation of large data sets, such as the OAI, with an accuracy equivalent to that achieved with supervised, semi-automated segmentation methods.

REFERENCES: [1] Losina et al. Ann Intern Med 2009, [2] Ronneberger et al. MICCAI 2015, [3] Kemnitz et al. MAGMA 2017, [4] Culvenor et al. Arthr Rheumat 2018, [5] Andrews et al. IEEE Trans Med Im 2015

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DICLOSURE STATEMENT: Chondrometrics (J. Kemnitz, W. Wirth, F. Eckstein)
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FULLY-AUTOMATED SEGMENTATION OF KNEE JOINT ANATOMY USING A DEEP CONVOLUTIONAL NEURAL NETWORK APPROACH

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INTRODUCTION: Segmentation is the crucial first step in the process to acquire quantitative measures of knee joint degeneration from magnetic resonance (MR) images in osteoarthritis (OA) research studies. Fully automated segmentation methods have primarily focusing on bone and cartilage with no previously described approach for segmenting all knee joint structures that may be sources of pain in OA patients.

OBJECTIVE: We hypothesize that a new fully-automated deep learning method would have similar accuracy for performing comprehensive tissue segmentation of the knee joint as manual labeling.

METHODS: The fully-automated deep learning approach is composed of an encoder-decoder (CED) network. The encoder network is the same as the 13 convolutional layers of the VGG16 network. The decoder network is a reverse process of the encoder and consists of up-sampling layers to recover high resolution pixel-wise labels. The final layer of the decoder network is a multi-class soft-max classifier for producing voxel-wise class probabilities. A fully connected three-dimensional (3D) conditional random field (CRF) is applied to optimize the label assignment for voxels with similar image intensity values and to take into account the 3D contextual relationships among voxels. 3D deformable modeling is implemented to maintain a smooth and well-defined boundary between cartilage and bone. The segmentation method was evaluated on sagittal fat-saturated 3D fast spin-echo (FSE) knee image datasets of 20 OA patients for segmenting 13 classes (12 different joint structures and one background class) using leave-one-out cross validation. To evaluate the accuracy of tissue segmentation, the Dice's coefficient was used for each individual joint structure to compare the segmentation result against manual labeling.

RESULTS: Deep learning tissue segmentation was fast with a mean computing time of 0.2 min, 0.8 min, and 3 min for the CED, the 3D fully-connected CRF, and the 3D deformable modeling process respectively for all image slices. The approach led to high segmentation accuracy, with Dice's coefficients for comparison with manual labelling over 0.9 for the femur, tibia, and muscle; between 0.8-0.9 for the femoral cartilage, tibial cartilage, patella, patellar cartilage, meniscus, quadriceps and patellar tendon, and infrapatellar fat pad; and between 0.7-0.8 for joint effusion and Baker's cyst (Figure).

CONCLUSION: Our study demonstrated the feasibility of using a fully-automated deep learning approach for efficient and accurate segmentation of all joint structures in patients with knee OA. Our results serve as a first step to provide quantitative MR measures of musculoskeletal tissue degeneration in a highly time efficient manner which would be practical for use in large population based OA research studies.

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DISCLOSURES: R. Kijowski is a consultant for GE Healthcare and Boston Imaging Core Lab
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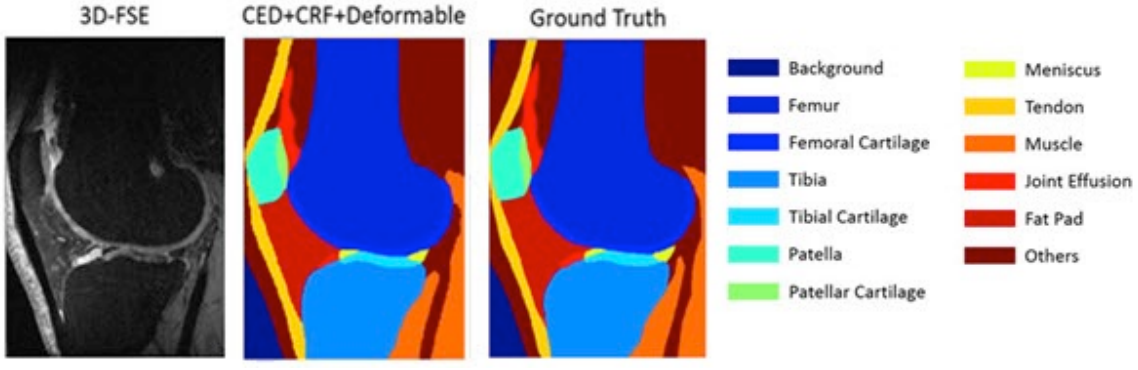

KNEE SEGMENTATION BY MULTIPLANAR DEEP LEARNING NETWORK – WITH DATA FROM THE OAI

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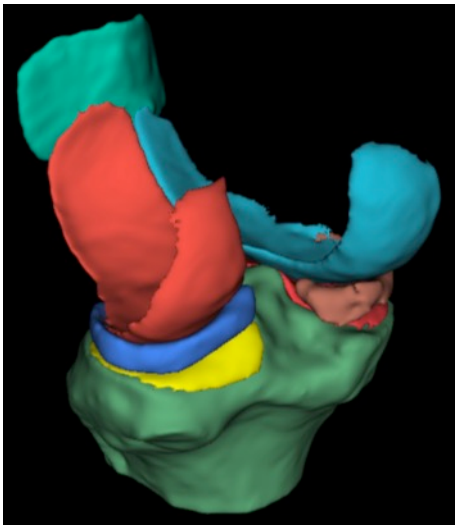
PURPOSE: AI and particularly Deep Learning methodologies are receiving much attention. We validated a fully automatic convolutional neural network originally developed for brain MRI segmentation for the task of knee MRI segmentation.

METHODS: We analyzed the subset of 88 baseline knee MRIs from the Osteoarthritis Initiative (OAI) with semi-manual segmentations including patellar and medial/lateral tibial/femoral cartilages, medial/lateral menisci, and the Tibia. Using 44 scans; we trained a multi-planar convolutional neural network with a U-net inspired architecture. The remaining 44 scans were used for validation. We quantified segmentation performance by the Dice volume overlap for cartilages and menisci.

RESULTS:

Dice Volume Overlap (mean + std)		
Comp.	Training (n=44)	Validation (n=44)
Bone		
Tibia	0.98+0.00	0.98+0.00
Cartilages		
MT	0.85+0.05	0.83+0.08
LT	0.89+0.03	0.87+0.06
MF	0.88+0.02	0.84+0.05
LF	0.90+0.02	0.87+0.04
P	0.84+0.07	0.80+0.12
Menisci		
MM	0.84+0.05	0.80+0.08
LM	0.88+0.02	0.86+0.03



DISCUSSION: Deep Learning networks are potentially prone to overfitting and poor generalization. By using a network designed for brain MRI we eliminated **method overfitting**. Our evaluation showed similar performance on training and validation sets, albeit demonstrating slight **parameter overfitting**. Extending the training set with the corresponding 1 year scans and performing cross-validation (e.g. 5 fold CV) will both increase the training set size and very likely reduce this parameter overfitting. These results and previous work indicate that validation performance very close to the given training performance is feasible and that this is very likely very close to the limit of the information content in this cohort. Segmentation time is approximately 2 minutes making the method applicable in clinical workflows. As demonstrated, our network is robust for the small, homogeneous data set. Further validation will evaluate the performance on larger, heterogeneous cohorts.

CONCLUSION: The study demonstrated the feasibility of accurate, fast, automatic knee MRI segmentation.

SPONSORS: None
DISCLOSURE: Erik Dam is a shareholder of Biomediq. The IPR for KIQ is with Biomediq.
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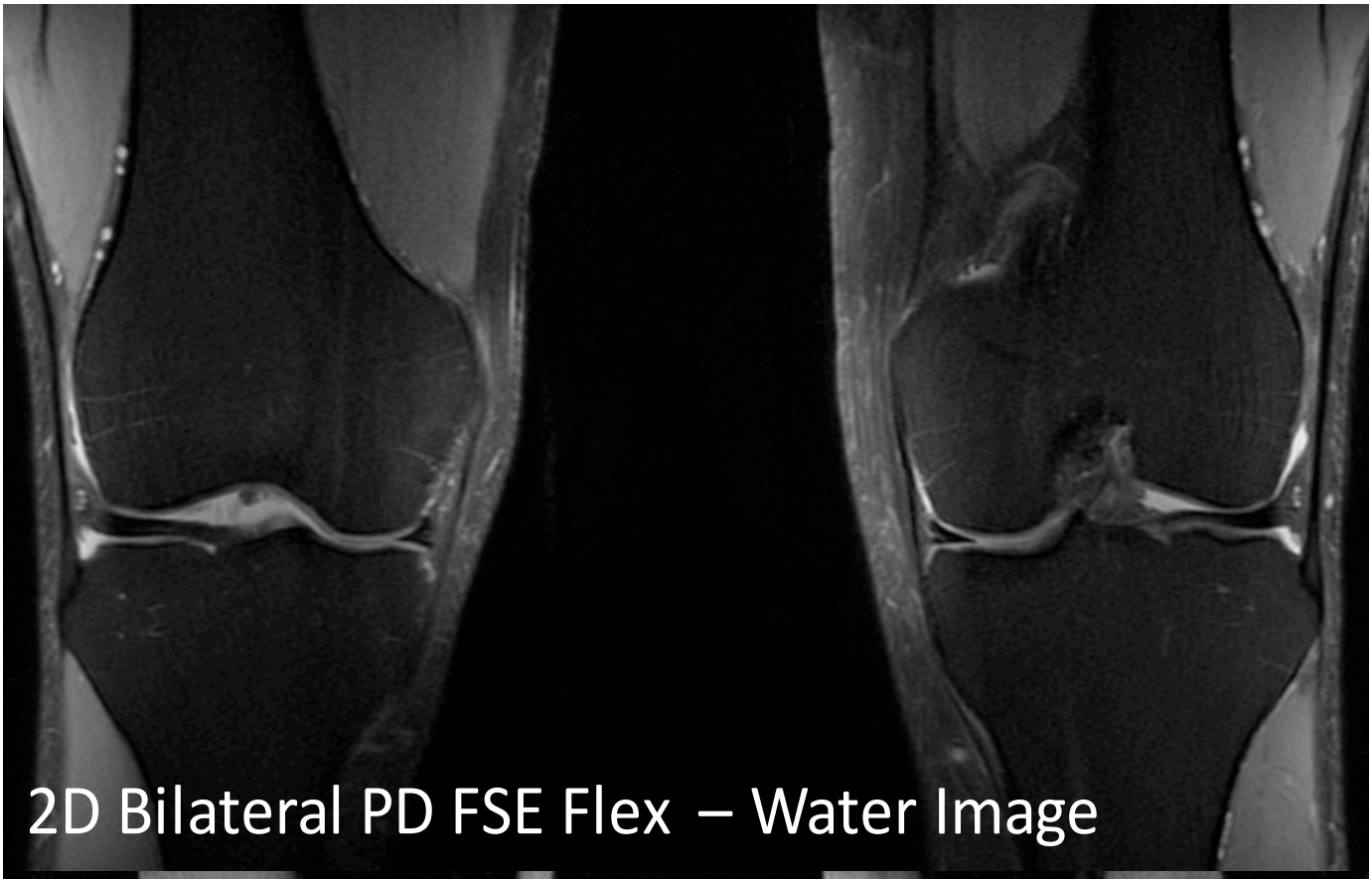
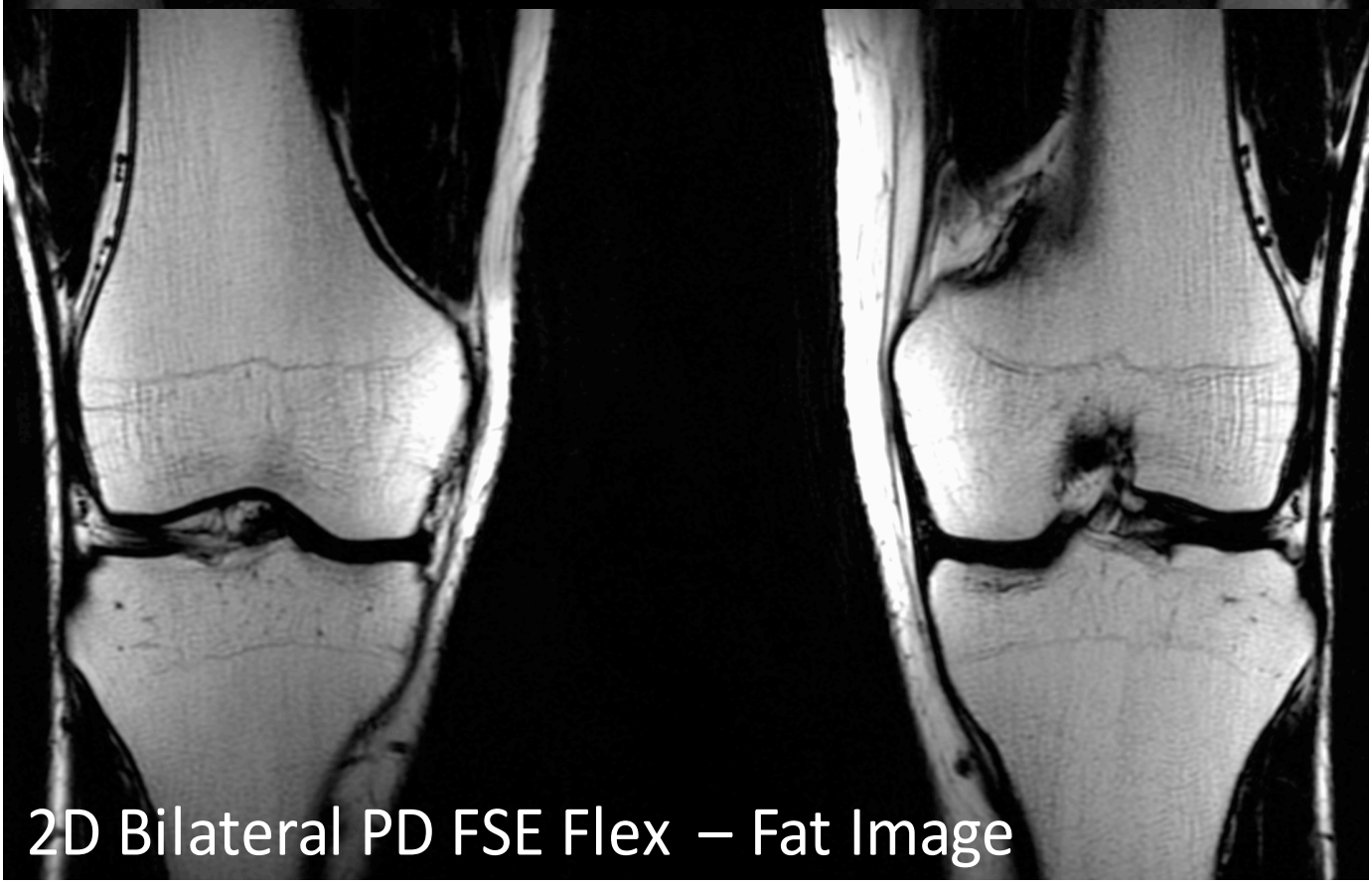

2D Bilateral PD FSE Flex – Water Image


2D Bilateral PD FSE Flex – Fat Image

THREE-DIMENSIONAL MRI FOR THE DEPICTION OF KNEE MENISCAL INJURIES: A METAANALYSIS DIAGNOSTIC PERFORMANCE

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INTRODUCTION: Over the last three decades, the image quality of three-dimensional (3D) magnetic resonance imaging (MRI) sequences has improved due to the development of more efficient acquisition and reconstruction techniques, and recent studies showed that the diagnostic performance of 3D sequences is comparable to currently used 2D fast spin-echo sequence for comprehensive knee joint assessment. However, there is still an ongoing debate whether 3D sequences could replace conventional 2D sequences for evaluating the knee joint in routine clinical practice.

OBJECTIVE: To assess the diagnostic performance of 3D MRI for detecting meniscal injuries using arthroscopy and/or open surgery as the standard of reference.

METHODS: A literature search was performed to identify original studies published between January 1985 and March 2018. Summary receiver operating characteristic (sROC) curve and sensitivity analysis were performed to compare the diagnostic performance of 3D versus two-dimensional (2D) MRI and to evaluate the impact of relevant co-variates on the diagnostic performance.

RESULTS: Out of 1759 identified records, 31 studies (1861 3D knee MRIs) were included (24 studies also reported the results of 2D MRIs). Pooled estimate of sensitivity (89.7% (95% confidence interval: 86.7%-92.1%) vs 88.5%(85.3%-91.1%);p=0.3), specificity (89.8% (86.9%-92.1%) vs 89.5% (86.2%-92.1%);p-value=0.99) and area under the curve (AUC) (0.96 (0.93-0.97) vs 0.95 (0.93-0.97);p=0.5) were similar using 3D compared to 2D MR imaging, respectively. Fast/turbo spin-echo (FSE/TSE) based 3D sequences demonstrated similar diagnostic performance compared to gradient-echo (GRE) based 3D sequences, except more sensitivity for detection of lateral meniscal tears (FSE:85.5 (75.8-91.8); GRE:74 (66-81);p=0.001). 3D MR imaging with multi-planar reformation (MPR) had slightly higher specificity (90.4 (86.8-93.1) than 2D (87.9 (83.1-91.4)) acquired in conventional planes (P=0.01).

CONCLUSION: Both FSE/TSE and GRE based 3D sequences have overall similar diagnostic performance compared to 2D MR imaging for detection of medial and lateral meniscal injuries, with slight superior sensitivity of FSE/TSE 3D sequences compared to GRE based 3D sequences for lateral meniscal injuries. MPR improve the specificity of the 3D MR imaging compared to 2D MR imaging.

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DISCLOSURE STATEMENT: F. Roemer is Shareholder of BICL, LLC. A. Guermazi is Shareholder of BICL, LLC and Consultant to Pfizer, TissueGene, OrthoTrophix, AstraZeneca, Sanofi, GE Healthcare and MerckSerono
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MECHANICAL STRESS AROUND CYSTS IS RELATED TO KNEE PAIN IN PATIENTS WITH KNEE OSTEOARTHRITIS: A SUBJECT-SPECIFIC FINITE ELEMENT STUDY

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INTRODUCTION: Subchondral cysts are a commonly observed, but poorly understood, feature of knee osteoarthritis (OA). McErlain et al (2011) postulated that local subchondral bone cyst presence increases intra-osseous stress distributions, leading to pain and disability. The association between cysts and OA-related pain is however unclear. Subject-specific finite element (FE) modeling is a non-invasive technique able to estimate internal bone stress and strain distributions by incorporating regional variations in bone structure, material properties, and geometry as well as accounting for limb alignment. FE modeling has not yet been used to compare cyst stress between individuals with varying OA-related knee pain.

OBJECTIVE: The objective of this study was to compare FE-derived mechanical stress around cysts from patients with differing levels of OA-related knee pain to those reporting no knee pain.

METHODS: The preoperative knee of 33 total knee replacement patients was scanned using quantitative CT. Pain was measured using the WOMAC and participants were categorized into three groups based on their pain score while lying in bed at night: 'no nocturnal pain' (score of 0 to 1), 'moderate nocturnal pain' (score of 2), and 'severe nocturnal pain' (score of 3 or 4) as based on our previous study evaluating subchondral BMD (Burnett et al., 2015). Cysts were identified in the proximal tibia CT images as approximate elliptical or spherical volumes of lower greyscale surrounded by higher greyscale through visual inspection guided by subject-specific half-maximum-height threshold values, then manually segmented. Only cysts within the subchondral region (depth of 7.5mm from the proximal tibia subchondral surface) were evaluated. We used subject-specific FE modelling with the leg in a neutral position to acquire von Mises stress of the proximal tibia. The volume around each cyst (1.25mm thickness) was used for assessing cyst stress. Cyst stress was evaluated over total, medial, and lateral subchondral regions of the proximal tibia. We contrasted von Mises stress around cysts in the moderate and severe nocturnal pain groups to that in the no nocturnal pain group using analysis of covariance (with age and sex as covariates).

RESULTS: von Mises stress around cysts at the lateral region was, on average, 86% higher in participants with severe pain than in participants with no pain (adjusted mean difference 0.35 MPa, 95% CI from 0.01 to 0.69). There were no differences in total or medial von Mises stress around cysts between pain and no pain groups.

CONCLUSION: Individuals with greater OA-related knee pain have greater stress placed upon bone surrounding cysts. Our findings suggest that OA pain may be due to stress approaching, or exceeding, bone tissue's yield strength. Alternately, pain may reflective of bone remodeling to support higher stress. These early results identify mechanical outcomes to target when investigating the role of bone in OA-related pain, and emphasize the importance of evaluating bone mechanics in OA-related pain pathogenesis.

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DISCLOSURE STATEMENT: None
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OPEN-SOURCED DEEP-LEARNING FOR CARTILAGE AND MENISCUS SEGMENTATION

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INTRODUCTION: Segmentation of tissues such as cartilage and menisci from 3D MRI data is essential for understanding variations in tissue morphology and composition in order to learn about OA progression[1]. However, tissue segmentation is a slow and cumbersome manual task where even expert readers can produce discordant results, which is not practical for large research studies. Advances in deep learning have the potential for enhancing the speed, accuracy, and robustness of automated segmentations[2,3]. Despite such advances, most automated methods are not open-sourced, which precludes the OA research community from fully utilizing such advances in deep learning.

OBJECTIVE: To (1) Use convolutional neural networks (CNNs) to perform state-of-the-art automated *segmentation of cartilage and meniscus* in the femorotibial joint, and (2) Make all training data as well as deep learning code and models *fully accessible* to the research community.

METHODS: We develop a 2D CNN (entitled Seg-CNN) for segmentation based on the U-Net model[3,4]. Seg-CNN utilizes 6 convolutional layers in the U-Net encoder and decoder each, with feature map lengths increasing in power of two from 32 to 1024 features per convolution. Network training was performed on 3D DESS sequences obtained from the OAI. 88 patients over two time points (baseline and 1 year) were split into 60/14/14 for training, validation, and testing, respectively. Unlike previous CNNs that trained on the baseline scan and tested on subsequent timepoints[3], testing for this study was performed on data not previously seen by the network. The training, validation, and testing groups were divided approximately equally by KLG to ensure minimal bias amongst the three datasets (Table 1). A dice coefficient (DC) loss function was used to train separate networks to segment the femoral and tibial cartilage (FC and TC), and the meniscus (Men) in the femorotibial joint. All datasets had manual segmentations available. DC and volume of cartilage coefficient of variation (VCCV) evaluated segmentation accuracy in the 28 knees.

KLG	Train	Valid	Test
1	2 (2%)	2 (7%)	0 (0%)
2	42 (35%)	8 (29%)	9 (32%)
3	80 (58%)	15 (54%)	16 (57%)
4	6 (5%)	3 (11%)	3 (11%)
Total:	120 (100%	28 (100%)	28 (100%)

Table 1: Knee KLGs used for Seg-CNN. Number in parentheses represents % of KLG in the specific group.

KLG	FC	TC	Men
2	89.8 ± 2.0	87.9 ± 2.3	76.0 ± 3.5
3	90.0 ± 1.3	85.6 ± 3.8	75.1 ± 4.2
4	90.1 ± 1.8	76.1 ± 1.9	75.8 ± 3.7
Total	89.9 ± 1.6	85.3 ± 4.7	75.4 ± 3.8
VCCV%	1.7 ±1.2	6.5 ± 5.8	9.0 ± 5.7

Table 2: Segmentation accuracy of Seg-CNN for segmentation of three tissues in the femorotibial joint.

RESULTS & DISCUSSION: DC scores of Seg-CNN segmentations exceed the current state of the art for cartilage and perform similarly for the meniscus[3], without reusing training data during testing. A VCCV of 2% for femoral cartilage is similar to that of manual inter-reader variability, while 6% for tibial cartilage is almost similar. A majority of the segmentation errors arose in determining the tissue start and end slices, which is easier to correct manually than altering in-plane segmentations. The duration required to segment the 3D DESS dataset for all three tissues was only 1.5 seconds. Source code and learned model weights are available to the OA research community at https://github.com/akshaysc/msk_segmentation.

CONCLUSION: We demonstrated state-of-the-art results for automated segmentation of the femorotibial joint using deep learning and will make this method public for pervasive integration in OA research studies.

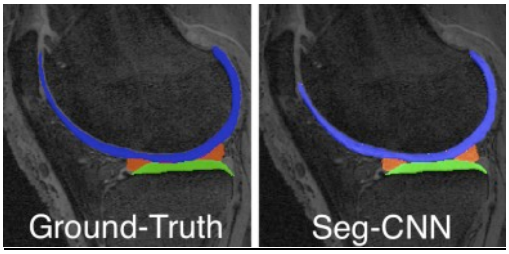

Fig. 1: Example segmentation of femoral (purple) and tibial (green) cartilage and meniscus (red).

REFERENCES: 1. Eckstein OAC 2006; 2. Liu MRM 2017; 3. Norman Radiology 2017; 4. Ronnenberger MICCAI 2015.

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DISCLOSURE: AC has consulted for Skope MR Technologies and Subtle Medical
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APPLICATION OF DEEP LEARNING FOR THE QUANTITATIVE ASSESSMENT OF BONE MARROW LESIONS

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INTRODUCTION: MRI can be used to assess several structural changes related to knee OA (KOA). Software image analysis methods provide objective fully quantitative measurements of these changes. However, such methods generally require a human reader and can be time consuming if the number of images in a study is large. Deep leaning (DL), a form of statistical machine learning, offers the potential for increased or full automation, therefore reducing reader time substantially.

OBJECTIVE: The goal of our study was to validate a DL method for segmenting (outlining) bone marrow lesions (BMLs) on knee MRI data sets.

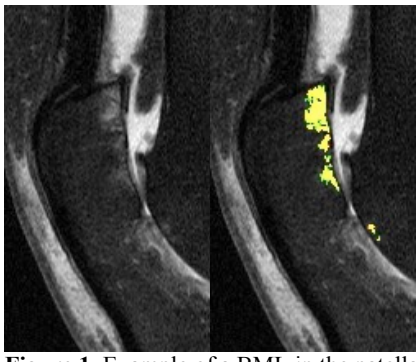

Figure 1. Example of a BML in the patella on MRI (left) and segmented (right). Yellow pixels are where DL and SA overlapped. Red and green pixels are areas of disagreement.

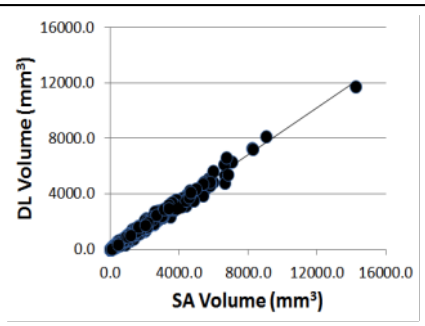

Figure 2. Plot comparing the SA to DL methods. Pearson's R^2 was 0.99

METHODS: We used the baseline and 24 month scans from the 600 subjects included in the FNIH Study, a nested case/control sub study of the OAI. Subjects in the sub-study were selected from four groups based on medial radiographically-assessed joint space loss (JSL) and pain progression. JSL progression was defined as medial tibiofemoral radiographic JSL≥0.7mm from baseline to 24, 36, or 48 months. Pain progression was defined as persistent increase on the WOMAC pain scale from 24 to 60 months. For the DL method, the reader was required to indicate the location of each BML, a step that requires less than 30 seconds of reader time per scan. The readings were performed on sagittal turbo spin echo fat-suppressed (TSE FS) MRI scans at the baseline and 24-month time points. The reader was fully blinded. BMLs segmented using a previously validated semi-automated (SA) method [1] were used to train the DL algorithm using a cross-validation technique. Once trained, the DL software was applied to the full data set to calculate volume and comparisons were made to the results from the SA method. Dice similarity coefficients (DSC) and Pearson's R^2 are reported. For clinical validation, we used logistic regression with odds ratios (OR) and 95% confidence intervals (CI) as metrics to assess the association of baseline to 24 mo. change in BML volume with progression status. Each model was adjusted for age, sex, BMI, and race. ORs were calculated per 1 standard deviation loss of cartilage from baseline to 24 months. In Figure 1 we show a representative example of BMLs segmented with SA and DL.

RESULTS: The average DSC was 0.85 and Figure 2 is a plot comparing the SA to the DL methods. The Pearson's R^2 was 0.99 and the slope was 0.85 indicating that the DL systematically underestimates the volume. The OR's (CI) for the SA and DL methods were 0.81 (0.67, 0.96) and 0.80 (0.68, 0.97) respectively.

CONCLUSIONS: The results suggest that the SA and LD methods are nearly equivalent for segmenting BMLs for KOA. The DL approach can produce a highly accurate method to assess BML volume that requires offers substantial time savings over the SA method. The 0.85 shift can easily be corrected. Future work will investigate a fully automated method, which does not require a reader to initially locate BMLs.

[1] Ratzlaff et al., Osteoarthritis and Cartilage (2013)

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KNEE JOINT DISTRACTION COMPARED WITH HIGH TIBIAL OSTEOTOMY AND TOTAL KNEE ARTHROPLASTY: TWO-YEAR CLINICAL, STRUCTURAL, AND BIOMARKER OUTCOMES

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INTRODUCTION: Knee joint distraction (KJD) is a joint-preserving surgery technique that, like high tibial osteotomy (HTO), aims to delay TKA especially in younger patients with knee osteoarthritis (OA). One year after treatment, KJD demonstrated similar beneficial outcomes compared to HTO and to TKA.

OBJECTIVE: 1) To compare radiographic joint space width and clinical outcome over two-years for KJD vs. TKA and for KJD vs. HTO and 2) to additionally study KJD cartilage repair by evaluation of systemic collagen type II markers.

METHODS: End-stage knee OA patients considered for TKA were randomized to KJD (n=20; KJD_{TKA}) or TKA (n=40). Medial compartmental knee OA patients with a varus deviation of <10° considered for opening wedge HTO were randomized to KJD (n=23; KJD_{HTO}) or HTO (n=46). Distraction surgery was performed by use of two external fixators with built in springs, placed lateral and medial of the knee joint. The knee was distracted 5 mm for 6 weeks and weight-bearing was encouraged.
WOMAC questionnaires (100 best) and VAS pain scores (0 best) were assessed at baseline (0), 3, 6, 12, 18 and 24 months. In the KJD groups, serum PIIANP and urine CTXII levels, as markers for collagen type II synthesis and breakdown, were determined over time. Normalized Z-indexes were calculated ($Z_{index} = Z_{PIIANP} - Z_{CTXII}$) to express net collagen type II synthesis. The minimum and mean joint space width (JSW) of the most affected compartment (MAC) were measured with KIDA software on standardized radiographs taken at 0, 12 and 24 months.

RESULTS: Of the 129 included patients, 15 patients were lost in the KJD_{TKA} (1), TKA (6), KJD_{HTO} (3), and HTO (5) group respectively, for various reasons. One-year structural and clinical outcomes were statistically significantly improved as reported before, and these beneficial effects sustained for at least two years after treatment when compared to baseline. At 24 months, there were no significant differences between the KJD_{HTO} and HTO groups (all $p>0.25$) and between the KJD_{TKA} and TKA group, except for the VAS pain score in favor of TKA at 24 months ($p=0.037$).
Compared to baseline, the ratio of synthesis over breakdown of collagen type II biomarkers was significantly decreased at 3 months (-0.45±0.20; $p=0.032$) after which this reversed towards an increase over time (at 24 months +0.59±0.19; $p=0.004$).

CONCLUSION: Sustained improvement of clinical benefit and increase in JSW after KJD is demonstrated for over 2 years of follow-up in case of treatment of patients with medial compartmental knee OA indicated for HTO or patients with end-stage knee OA indicated for TKA. The structural cartilage repair observed on radiographs is supported by a beneficial change in systemic biomarkers for collagen type II. For the HTO-indicated population, results of KJD patients were similar to those of HTO. For the TKA-indicated patients, TKA appeared to result in a slightly better clinical outcome, however at the expense of the native knee joint.

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DISCLOSURE STATEMENT: FPJG Lafeber is co-founder, co-director, and shareholder of ArthroSave BV, a medical device company involved in marketing a user-friendly knee joint distraction device
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THE RELATIONSSHIP BETWEEN IMAGING BIOMARKERS AND KNEE REPLACEMENT IS AS STRONG AS THAT FOR PATIENT REPORTED OUTCOMES (PROS) OF KNEE PAIN SYMPTOMS

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INTRODUCTION: OA meets the 2014 revised FDA definition of a "serious" disease [1], potentially allowing for an accelerated approval path for DMOADs. To that end, a relatively short clinical trial may be performed using a surrogate biomarker endpoint, with a longer post-approval phase required to ensure improvement in patient-related outcomes (PROs) or knee replacement (KR) rates as a "hard" clinical endpoint. When used for drug approval, the surrogate biomarker needs to be "qualified", however, i.e. its change must be reasonably likely be related to a relevant clinical outcome. Current FDA guidelines recognize changes in mJSW as structure modification as 3-year change in mJSW has been shown to be related to future KR [2]. Cartilage thickness change by MRI was recently shown to yield similar associations with KR as fixed location JSW [fJSW]) over 2 years, but area under the curve (AUCs) values were only of modest magnitude [3].

OBJECTIVE: To compare discrimination of subsequent KR vs. non-KR status by 2-year change in radiographic (Rx) JSW, MRI cartilage thickness, and commonly utilized PROs of knee symptoms in the same sample.

METHODS: Knees replaced between 36 and 60 months' follow-up in the Osteoarthritis Initiative (OAI) were each matched with one control by baseline KLG, age, and sex [3]. Rx JSW was determined from fixed flexion radiographs and medial femorotibial compartment (MFTC) cartilage thickness (ThC) from 3T MRI [3]. Clinically relevant symptom PROs included WOMAC knee pain, function, KOOS QoL, and NRS pain (last month). Changes between the annual visit before replacement (T0) and 2 years before T0 (T-2) were compared between KR case and non-KR control knees using case-control conditional AUCs (ccAUCs).

RESULTS: 119 knees of 102 participants (55.5 % women; age 64.2 ± 8.7 y [mean ± SD]) were studied. The 2-year change in mJSW had the lowest ccAUC (0.59), whereas the fJSW and MRI measures yielded ccAUCs between 0.62 and 0.68 (central medial tibia [cMT] and total subregional change score). The 2-year changes in PROs (WOMAC pain, function, KOOS QoL, and NRS pain) resulted in comparable AUCs (0.66-0.71).

Table 1: 2-year change in radiographic (Rx), MRI measures and WOMAC pain predicting KR

	Cases		Controls		Comparison		
	Mean	SD	Mean	SD	ROC (ccAUC)	95% CI	
Rx mJSW (µm)	-415	1008	-133	621	0.59	0.52	0.66
Rx fJSW225 (µm)	-610	1059	-162	650	**0.66**	0.59	0.73
MRI MFTC ThC (µm)	-223	372	-95	189	0.62	0.55	0.69
MRI cMFTC ThC (µm)	-410	644	-142	289	0.66	0.59	0.72
MRI cMT ThC (µm)	-178	249	-57	155	**0.68**	0.61	0.74
MRI Change Score (µm)	2590	2182	1600	610	**0.68**	0.62	0.75
WOMAC Pain (0 to 20)	2.1	4.0	-0.3	3.2	0.66	0.60	0.73
WOMAC Ftn (0 to 68)	6.9	12.2	-1.1	8.9	0.70	0.64	0.77
KOOS QoL (0 to 100)	-7.8	20.6	4.7	16.1	**0.71**	0.64	0.77
NRS Pain (m) (0 to 10)	1.54	2.97	-0.06	2.50	0.66	0.60	0.73

CONCLUSIONS: The predictive relationship between imaging biomarkers (MRI cartilage thickness and fJSW) and surgical KR appears to be comparable to that of PROs commonly used as symptomatic endpoints in clinical trials. These results are surprising, as symptoms (PROs) and to some extent also radiographic change, are thought to be key factors in surgical KR decision making. Our findings suggest that MRI cartilage thickness change is as good a predictor of KR as symptom-related PROs, and hence likely represents a reasonable surrogate biomarker of knee OA progression for potential accelerated approval of DMOADs.

REFERENCES: [1] https://www.oarsi.org/research/oa-serious-disease; [2] Bruyere O et al. Ann Rheum Dis 2005;64:1727; [3] Eckstein F et al. Eur Radiol 2016;26:1942
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SHORT-TERM STRUCTURAL PROGRESSION ON MRI IS RELATED TO INCIDENT RADIOGRAPHIC AND CLINICAL KNEE OA, BUT IS IT RELEVANT FOR PREDICTION?

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INTRODUCTION: To potentially shorten osteoarthritis (OA) trials, imaging biomarkers of short-term structural progression that are predictive for future knee OA development are urgently needed.

OBJECTIVE: To evaluate the associations between 2.5 years progression in structural features on MRI and radiographic and clinical knee OA development after 6.5 years in a high-risk group of overweight and obese women, free of clinical and radiological knee OA at baseline.

METHODS: All women with complete 6.5 year data in the PROOF study were selected. All available baseline and 2.5 years MRI scans were evaluated using MOAKS and automatically segmented using the KneeIQ framework to determine medial tibiofemoral (TF) and patellar (PF) cartilage cavity (volume of summed over detected indentations) and mean cartilage thickness (for PF, entire medial TF compartment and for the weight-bearing central part). Using GEE, unadjusted associations between structural progression on MRI during the first 2.5 year interval and incident radiographic (KL $\geq$ 2) and incident clinical (ACR-criteria) knee OA after 6.5 years were determined. Pre-test and post-test probabilities were calculated for each MOAKS feature and each outcome.

RESULTS: 463 knees from 235 women were selected (mean age 55.7 ± 3.1 years, mean BMI 31.9 ± 3.8 kg/m^2). Odds ratios and 95% CIs, the pre- and post-test probabilities for each structural feature and for both outcomes are presented in the table (bold ORs indicate significance for $p < 0.05$).

Biomarker progression	Location	Incident radiographic OA			Incident clinical OA		
		Odds ratio	Pre-test	Post-test	Odds ratio	Pre-test	Post-test
BMLs	TF med	**4.9 (2.5-9.5)**	14,3% (58/407)	41,2% (14/34)	2.4 (0.9-6.4)	10,5% (43/411)	24,2% (8/33)
	TF lat	**2.5 (1.0-5.8)**	14,9% (63/422)	33,3% (10/30)	1.2 (0.4-3.3)	10,7% (46/429)	10,3% (3/29)
	PF	1.4 (0.8-2.5)	14,4% (56/390)	17,1% (18/105)	1.0 (0.5-2.1)	10,3% (41/398)	10,2% (11/108)
Cartilage defects	TF med	**3.8 (1.6-8.9)**	15,2% (66/434)	43,8% (14/32)	2.0 (0.8-4.7)	10,3% (45/438)	17,1% (6/35)
	TF lat	1.6 (0.5-4.9)	15,1% (66/438)	24,0% (6/25)	1.9 (0.8-4.5)	10,8% (48/444)	16,0% (4/25)
	PF	1.6 (1.0-2.7)	15,1% (64/424)	20,6% (21/102)	1.1 (0.6-2.1)	10,5% (45/430)	9,7% (10/103)
Meniscus pathologies	Med	1.3 (0.8-2.4)	15,0% (64/428)	16,9% (14/83)	1.3 (0.7-2.3)	11,1% (48/433)	12,8% (11/86)
	Lat	**2.2 (1.0-4.7)**	15,0% (64/427)	30,0% (12/40)	0.7 (0.2-2.2)	11,1% (48/433)	9,5% (4/42)
Meniscal extrusion	Med	**2.1 (1.1-4.0)**	14,5% (61/422)	24,6% (17/69)	1.1 (0.5-2.3)	11,0% (47/427)	11,4% (8/70)
	Lat	2.7 (0.9-7.7)	14,7% (64/434)	28,6% (4/14)	1.2 (0.3-4.9)	10,9% (48/439)	7,7% (1/13)
Osteophytes	TF med	**6.3 (3.0-13.2)**	14,9% (65/436)	47,5% (19/40)	**2.4 (1.2-4.9)**	10,6% (47/442)	22,2% (10/45)
	TF lat	**9.5 (3.2-27.5)**	14,9% (65/436)	66,7% (10/15)	**3.7 (1.4-10.0)**	10,9% (48/440)	31,8% (7/22)
	PF	**5.3 (2.4-11.7)**	15,0% (65/434)	50,0% (15/30)	1.6 (0.6-4.4)	10,5% (46/439)	15,2% (5/33)
Cartilage thickness	TF med	1.2 (0.8-2.0)	15,0% (63/419)	16,3% (33/202)	**2.0 (1.1-3.6)**	10,9% (46/423)	14,0% (29/207)
	TF med cent	1.4 (0.9-2.4)	15,0% (63/419)	16,8% (41/244)	1.9 (0.9-3.7)	10,9% (46/423)	13,3% (33/249)
	PF	1.0 (0.6-1.6)	15,0% (63/419)	15,0% (32/213)	1.6 (0.9-2.9)	10,9% (46/423)	12,8% (27/211)
Cartilage cavity	TF med	**0.6 (0.3-0.9)**	15,0% (63/419)	10,8% (20/186)	0.7 (0.4-1.1)	10,9% (46/423)	9,6% (18/188)
	PF	1.1 (0.7-1.8)	15,0% (63/419)	15,6% (33/212)	1.0 (0.6-1.9)	10,9% (46/423)	10,5% (23/219)

BMLs: bone marrow lesions. TF: tibiofemoral compartment. PF: patellofemoral compartment. Med: medial. Lat: lateral. Centr: central region

CONCLUSION: Despite several significant associations for different structural features and both outcomes, only few features actually lead to a substantially increased post-test probability. Nevertheless, most post-test probabilities remain relatively low limiting their relevance as imaging biomarkers of short-term structural progression.

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INTRA-ARTICULAR SPRIFERMIN IN SYMPTOMATIC RADIOGRAPHIC KNEE OSTEOARTHRITIS: A POST-HOC MULTI-TISSUE ANALYSIS OF MRI-DEFINED CHANGE OF THE 2-YEAR DATA FROM A 5-YEAR RANDOMIZED, PLACEBO-CONTROLLED, PHASE II STUDY

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INTRODUCTION: Sprifermin, a recombinant human fibroblast growth factor 18, is currently being investigated as a potential disease-modifying osteoarthritis (OA) drug. Recently, a dose-dependent increase in femorotibial cartilage thickness, as well as medial and lateral compartment cartilage, over two years was reported[1].

OBJECTIVE: The aim of this post-hoc analysis is to evaluate potential effects of sprifermin on additional structure endpoints, based on semi-quantitative MRI assessment over 24 months.

METHODS: Patients aged 40–85 years with symptomatic radiographic knee OA, KLG 2 or 3, and medial mJSW ≥2.5 mm in the target knee were randomized (1:1:1:1:1) to receive double-blinded placebo or sprifermin (30 µg or 100 µg), administered as 3 weekly intra-articular injections in cycles every 6 or 12 months. 1.5T or 3T MRIs were acquired at baseline, 6, 12, 18 and 24-month follow-up visits using a standard protocol (ClinicalTrials.gov identifier: NCT01033994). MRIs were read using the Whole-Organ Magnetic Resonance Imaging Score (WORMS) system (time points of baseline, 12 and 24 months) by three trained musculoskeletal radiologists. Analyses of all sprifermin and placebo arms included multiple MRI-defined osteoarthritis features and multi-dimensional assessments: (a) delta-subregional approach (the difference in the *number of subregions* with worsening as compared to improvement) and (b) delta-sum approach (absolute *scores of all subregions).* Analyses were performed on a whole knee level and separately for medial, lateral, and patellofemoral compartments. To test for potential dose-response effects, Jonckheere-Terpstra (asymptotic) test was used. P-values were not adjusted for multiple testing.

RESULTS: 549 patients were included. Dose-dependent treatment effect on cartilage morphology (i.e., less cartilage damage) was observed for the entire knee from baseline to 24 months using both delta sum (Placebo 1.61 (0.89, 2.34), Sprifermin 30 mcgx2 1.78 (1.25, 2.32), Sprifermin 30 mcgx4 1.20 (0.66, 1.74), Sprifermin 100 mcgx2 1.31 (0.82, 1.79), Sprifermin 100 mcgx4 0.98 (0.57, 1.38), p= 0.0384) and delta subregion approaches (Placebo 0.79 (0.49, 1.09), Sprifermin 30 mcgx2 0.90 (0.65, 1.15), Sprifermin 30 mcgx4 0.60 (0.37, 0.83), Sprifermin 100 mcgx2 0.59 (0.39, 0.79), Sprifermin 100 mcgx4 0.55 (0.35, 0.76), p=0.0358). For bone marrow lesions (BMLs), a dose-dependent treatment effect (improvement of BMLs) was observed from baseline to 24 months for the patellofemoral joint using both delta sum (Placebo -0.10 (-0.30, 0.10), Sprifermin 30 mcgx2 -0.06 (-0.26, 0.13), Sprifermin 30 mcgx4 -0.13 (-0.34, 0.08), Sprifermin 100 mcgx2 -0.24 (-0.45, -0.03), Sprifermin 100 mcgx4 -0.26 (-0.50, -0.02), p= 0.0171) and delta subregion approaches (Placebo -0.05 (-0.22, 0.12), Sprifermin 30 mcgx2 -0.11 (-0.28, 0.07), Sprifermin 30 mcgx4 -0.11 (-0.30, 0.07), Sprifermin 100 mcgx2 -0.22 (-0.40, -0.04), Sprifermin 100 mcgx4 -0.28 (-0.46, -0.09), p= 0.0186) but not the other compartments. No significant effects were seen for baseline to 24-month changes in Hoffa-synovitis, effusion-synovitis, menisci, or osteophytes.

CONCLUSION: This post-hoc analysis indicates that sprifermin has a positive effect on cartilage morphology, in addition to the previously reported effect on cartilage thickness. Sprifermin was also associated with BML improvement in the patellofemoral joint. There were no significant effects associated with sprifermin on other joint tissues assessed, and no safety concerns raised.

REFERENCES: [1]Hochberg MC et al. *Arthritis Rheumatol* 2017; 69 (suppl 10).

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COMMUNICATING CLINICAL RELEVANCE OF AN IMAGING BIOMARKER WITH PROBABILITY: PREDICTING KNEE REPLACEMENT WITH TOTAL CARTILAGE THICKNESS

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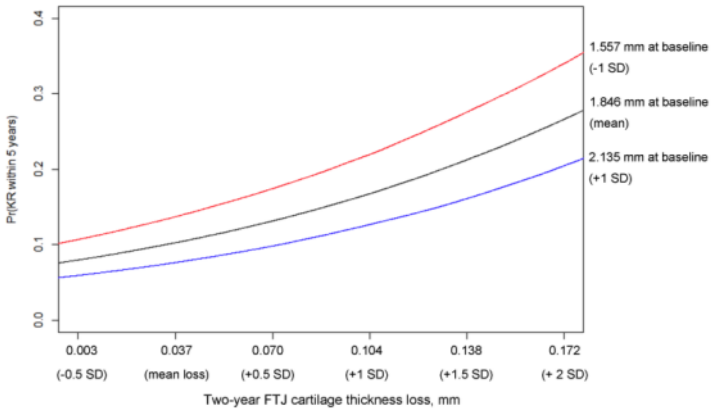
INTRODUCTION: Establishing a threshold of clinically important cartilage loss is of great interest for the design and interpretation of knee OA trials of structure-modifying treatments.

OBJECTIVE: Obtain predictive probabilities of knee replacement based on femorotibial joint cartilage thickness at baseline and cartilage thickness loss over 2 years.

METHODS: Knees with symptomatic OA, defined by definite osteophyte (OARSI atlas grade 1-3, based on clinical center screening reading) and participant-reported frequent knee symptoms at baseline, were selected prospectively from the OAI (Project 09B). Total femorotibial joint (FTJ) cartilage thickness at baseline and year 2 were measured on quantitative MRI (3T; sagittal DESS sequence) and calculated as total volume divided by surface area (VCtAB). Knee replacements reported up to 7 years following the 2-year imaging window were self-reported and confirmed. We used a Bayesian discrete time logistic survival model with intercepts (α_k) for each year of follow-up: $\text{logit}[p_k(x)] = \alpha_k + \beta' x$. Diffuse reference prior distributions for the model parameters, α_k, $\beta_j \sim N(0, 10^4)$ were specified. Posterior densities of the regression coefficients were estimated with 10,000 Markov Chain Monte Carlo (MCMC) samples generated with the R package R2OpenBUGS. Models with and without baseline and 2-year cartilage loss measures were compared with the deviance information criteria (DIC). Sensitivity of the results to the prior specification was considered.

RESULTS: Among 582 knees (one knee per participant), 95 underwent KR up to 7 years following the initial 2-year imaging window (median follow-up 6 years). Mean baseline cartilage thickness was 1.846 mm (SD 0.289), while mean loss of cartilage over 2 years was 0.037mm (SD 0.067). Greater cartilage thickness at baseline (standardized) was associated with lower odds of KR (OR=0.73 [95% credible interval (CI): 0.59, 0.90]; Pr(OR<1 | data) = 0.9995). 2-year loss of cartilage thickness (standardized) was associated with greater odds of KR (OR=1.71 [95%CI: 1.41, 2.05]; Pr(OR>1| data) =1.0).

The figure presents predictive probabilities of KR as a function of 2-year cartilage thickness loss for three baseline cartilage thickness values. For example, a knee with mean baseline cartilage thickness 1.846 mm and 2 year loss of 0.172 mm has a probability of KR within 5 years of 0.27. A knee with less baseline cartilage, 1.557 mm(-1SD), has a probability of KR of 0.34 with the same measured loss, while a knee with greater thickness at baseline, 2.135 mm(+1SD), has probability of KR of 0.20.



CONCLUSIONS: The same quantity of 2-year loss of FTJ cartilage thickness has varying predictive probability of future knee replacement depending on the amount of baseline cartilage thickness, highlighting the difficulty of defining minimum clinically important differences (MCIDs). Predictive probabilities of clinically relevant outcomes provide a more interpretable way to communicate the clinical relevance of imaging biomarkers beyond traditionally reported odds ratios.

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ASSOCIATION BETWEEN GOUT AND MRI-BASED KNEE OSTEOAARTHRITIS WORSENING: PRELIMINARY ANALYSIS FROM THE FNIH STUDY

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INTRODUCTION: To date, a limited number of studies investigated the association between gout and knee osteoarthritis (OA) progression, and findings are conflicting. Despite the suggested relationship between these two highly prevalent and chronic medical conditions, it is unclear whether the presence of gout could accelerate the pathogenesis of OA.

OBJECTIVE: To determine whether the presence of gout is associated with increased odds of knee OA worsening in participants of the Foundation of the National Institute of Health (FNIH) study.

METHODS: Using 1:3 propensity score matching method, 25 subjects with positive history of physician confirmed gout (symptomatic and/or subclinical gout in any joints) and 75 controls who were matched for OA and gout confounding variables (age, sex, BMI, and race) were included in this IRB approved HIPAA compliant study. Baseline and follow-up knee radiographic measurements and MRI Osteoarthritis Knee Score (MOAKS) variables for cartilage damage, bone marrow lesions (BMLs), osteophytes, effusion-synovitis, and Hoffa-synovitis were extracted. The association between gout and 48-months radiographic OA progression (>0.7mm reduction in medial tibiofemoral joint space width) was evaluated using conditional regression model. The relationship between gout and 24-months change in MOAKS measurements was determined using conditional regression. A mediation effect analysis was utilized to explore the variable mediating the association between gout and knee OA.

RESULTS: There was no significant association between gout and 48-months radiographic OA progression (OR 95%CI: 1.21 (0.66–2.21)). However, in comparison with matched controls, subjects with gout showed higher odds of worsening tibial cartilage damage (OR 95%CI: 2.02 (1.01–4.04)) and Hoffa-synovitis (OR 95%CI: 5.20 (0.89–30.48)), but not for osteophyte or BML worsening, over 24-months. Mediation analyses suggested a non-significant trend for the mediatory role of Hoffa-synovitis for the association between gout and tibial cartilage damage worsening (Sobel's test p-value: 0.086; indirect effect 95%CI: -0.084–2.087).

CONCLUSION: Positive medical history of gout is associated with longitudinal MRI-based OA-related structural damage worsening including tibial cartilage defect and Hoffa-synovitis. Presence of symptomatic or subclinical gout in any joints can be considered as a potential risk factor for future tibiofemoral OA progression.

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SCIENTIFIC POSTERS

IDENTIFICATION OF SUB-GROUPS OF PARTICIPANTS BASED ON PHYSICAL ACTIVITY, KNEE PAIN, BODY MASS INDEX AND SOCIO-ECONOMIC STATUS FOR KNEE OSTEOARTHRITIS: A POPULATION-BASED COHORT STUDY

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INTRODUCTION: The identification of sub-groups of participants with similar characteristics to reduce heterogeneity of factors, is important in understanding the development and progression of knee osteoarthritis.

OBJECTIVE: This study aimed 1) to identify sub-groups of participants based on physical activity (PA), knee pain, body mass index (BMI) and socio-economic status (SES) and 2) to investigate the association of these sub-groups with tibial cartilage volume, bone marrow lesions (BMLs) and knee replacements (KR) over 10.7 years.

METHODS: 1046 community-dwelling older adults aged 50 – 80 years were studied. At baseline, PA was measured by pedometers (steps/day), knee pain was assessed using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), BMI was obtained utilizing objective weight and height measures and SES was determined by the Socio Economic Indexes for Areas (SEIFA) scores. MRI scans were conducted at baseline and 10.7 years to assess tibial cartilage volume and BMLs. The incidence of KR was determined by data linkage to the Australian Orthopaedic Association National Joint Replacement Registry. Latent class analysis was used to determine sub-groups of participants based on PA, WOMAC pain, BMI and SES, at baseline. Linear mixed-effects models and log-binomial models were used to estimate the associations between the identified sub-groups and change in tibial cartilage volume, incident BMLs, and KR surgery. All models were adjusted for age, sex, and history of knee injury, while the KR model was additionally adjusted for the prevalence of knee radiographic osteoarthritis.

RESULTS: Three sub-groups/classes were identified: Class 1: Normal/overweight participants with low levels of PA, mild pain and low SES (32%); Class 2: Obese participants with low levels of PA, mild pain and moderate SES (27%); Class 3: Normal/overweight participants with high levels of PA, mild pain and high SES (41%). Mean cartilage volume loss over 10.7 years was 465±231 mm^3. 221 participants had an incident BML while 74 had an incident KR. Class 2 participants had greater cartilage volume loss over 10.7 years (β -61.8, 95% CI -121.7, -1.8) and, had a higher risk of KR (RR 1.99, 95% CI 1.08, 3.67), compared to Class 1 participants. Class 3 was not associated with cartilage volume change (β 6.5, 95% CI -41.1, 54.2) or risk of KR (RR 0.61, 95% CI 0.29, 1.29), compared to Class 1. Furthermore, these classes were not associated with incident BMLs (Class 2: RR 1.25, 95% CI 0.92, 1.69; Class 3: RR 1.29, 95% CI 0.97, 1.70; compared to Class 1).

CONCLUSION: This supports the benefit of identifying risk factors that cluster together and using them to identify sub-groups of people who may be at a higher risk of developing OA.

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ASSOCIATION OF HIP SHAPES WITH KNEE OSTEOARTHRITIS OUTCOMES IN OLDER-ADULTS

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INTRODUCTION: Various hip shapes may be important as a risk factor for development and progression of knee osteoarthritis, potentially due to the biomechanical link between the two joints.

OBJECTIVE: This study aims to identify the relationship between hip morphology and structural and clinical osteoarthritis outcomes in the knee, in older-adults.

METHODS: 377 community-dwelling older-adults aged 50–80 years were studied. At baseline, dual-energy X-ray absorptiometry images of the left hip were obtained and hip shapes were described using mode scores from an 85-point statistical shape model. MRI scans were conducted at baseline and a mean follow-up of 10.7(SD:0.67) years later, to assess right knee tibial cartilage volume and bone-marrow lesions(BMLs). Knee pain was assessed using Western Ontario and McMaster Universities Osteoarthritis Index(WOMAC). Knee replacement(KR) data were obtained by data linkage to the Australian Orthopaedic Association National Joint Replacement Registry. Linear mixed-effects, log-binomial models and survival analysis were used to investigate associations between hip shape modes and knee osteoarthritis outcomes adjusting for potential confounders.

RESULTS: Ten hip shape modes were identified, describing 78% of the total shape variance in descending order from mode 01 (31% variance) to mode 10 (1.82% variance). Hip shapes with a larger greater trochanter (mode 07) were associated with less knee cartilage volume loss (β: 2.14, 95% CI: 0.07,4.21), while a shorter and narrower femoral neck shape (mode 09) was related to increased volume loss (β: -3.86, 95% CI: -6.16, -1.56). Hip shapes with a non-spherical femoral head (mode 04) were associated with an increased risk of incident BMLs (RR: 1.19, 95% CI:1.07, 1.34). Those with a longer, wider femoral neck and a larger femoral head (mode 01) had an increased risk of worsening knee pain (RR: 1.33, 95% CI: 1.09, 1.61), whereas those with a smooth curving upper femoral neck (mode 09) had a lower risk of worsening knee pain (RR: 0.78, 95% CI: 0.67, 0.90). A larger greater trochanter and wider femoral neck shape (mode 08) was associated with an increased risk of KR (RR: 1.73, 95% CI: 1.18, 2.52), while increasing acetabular coverage (mode 10) was associated with a lower risk of KR (RR: 0.54, 95% CI: 0.36,0.8).

CONCLUSION: Hip shape variations were associated with significant MRI-based and clinical outcomes in the knee over 10.7 years, possibly due to biomechanical, lifestyle or other factors related to both joints. These results suggest that hip shape may play an important role in the onset and progression of knee osteoarthritis over time.

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DISCLOSURE STATEMENT: None.
ACKNOWLEDGEMENT: Study participants, and Catrina Boon and Pip Boon for data collection.
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MULTIPARAMETRIC MR IMAGING MAPPING TO QUANTIFY ARTICULAR CARTILAGE TISSUE FUNCTIONALITY - THE KEY TO DIAGNOSING EARLY OA?

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INTRODUCTION: Detection of early cartilage degeneration by clinical standard diagnostic tools remains elusive. Even though functional MRI (syn. quantitative [qMRI]) techniques (such as T1ρ, T2 and T2* mapping) provide information on the extracellular matrix beyond structure and morphology, these parameters have failed in the reliable diagnosis of early OA. Hence, biomechanical stimuli have been implemented within MRI scan protocols to assess cartilage tissue functionality as a potential marker of the tissue's status in health and disease.

OBJECTIVE: The aim of this study was to assess human articular cartilage tissue functionality by multiparametric qMRI as a function of histological degeneration. We hypothesized that 1) loading induces intra-tissue changes that are reflected by changes in the qMRI parameters and 2) that these changes in the qMRI parameters are related to the tissue's grade of histological degeneration.

METHODS: This study is an institutional review board-approved prospective comparative ex-vivo imaging study of 49 human articular cartilage samples obtained during total knee arthroplasties. Samples were placed in a standardized artificial knee joint within an MRI-compatible whole knee-joint compressive loading device and imaged at three consecutive displacement positions, i.e. unloaded (δ_0), at 2.5 mm displacement ($\delta_{2.5}$, i.e. 20 % body weight [BW]) and at 5 mm displacement ($\delta_{5.0}$, i.e. 110 % BW) (Fig. 1). Inversion recovery, spin-lock multi-gradient-echo, multi-spin-echo, and multi-gradient-echo sequences were acquired on a clinical 3.0T MRI system (Achieva, Philips) and used to generate serial T1, T1ρ, T2 and T2* maps for each sample and displacement position. Histological assessment (Mankin scoring) and biomechanical testing (Young's modulus) served as reference and samples were grouped as intact (Mankin sum scores 0-4) or early degenerative (scores 5-8). After log transformation, repeated measures ANOVA was used to detect longitudinal differences in qMRI parameters.

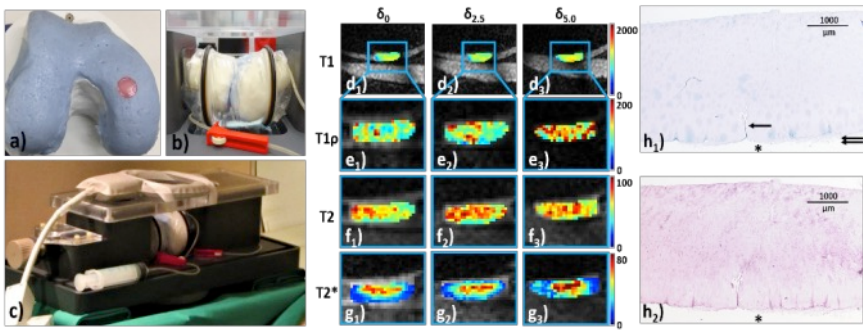

Fig. 1: Device for the standardized, displacement-controlled compressive loading of human articular chondral samples within a standardized knee joint, see Nebelung S et al., BMMB, 2017; 16(6):1971-86) for more details (a-c). Parameter maps in response to loading are displayed at consecutive displacement positions δ_0 (d_1-g_1), $\delta_{2.5}$ (d_2-g_2) and $\delta_{5.0}$ (d_3-g_3) and at higher magnifications (e-g) Corresponding histological sections (HE [h_1] and Safranin O staining [h_2] of early degenerative cartilage (Mankin sum score 8, Mankin Grade I).

RESULTS: Histologically, 27 samples were intact and 22 early degenerated. Mean pixel number and sample height decreased with loading. For T1ρ and T2*, significant loading-induced changes were found in the early degenerative subgroup only, while for T1 and T2, consistent and significant decreases in all zones (T1) as well as decreases in the superficial and increases in the deep zone (T2) were observed, regardless of degeneration.

CONCLUSION: Cartilage tissue functionality may be parameterized and quantified as a function of histological degeneration using qMRI parameter mapping under loading. Distinct differences in the response-to-loading patterns were found; thus, the non-invasive, MRI based monitoring of the tissue's ability to bear loads may provide a promising diagnostic target in the detection of early cartilage degeneration.

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ACKNOWLEDGEMENT: None.
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COMPUTATIONAL MODELING TECHNIQUES TO REFINE THE DIAGNOSTIC PROFILES OF QUANTITATIVE MRI PARAMETERS IN THE ASSESSMENT OF CARTILAGE

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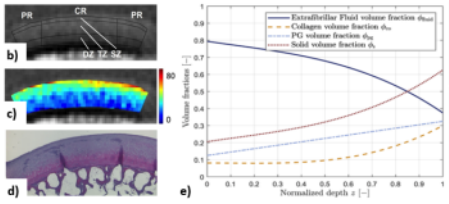
INTRODUCTION: Quantitative MRI (qMRI) techniques such as T1ρ, T2, T2* and T1 mapping are promising in the non-invasive assessment of cartilage. While providing quantitative information on the extracellular matrix constituents, these techniques' exact structural and/or compositional correlates remain to be defined.

OBJECTIVE: Further define each qMRI parameter's diagnostic profile in relation to distinct cartilage constituents using a constitutive numerical model of human cartilage. We hypothesized the qMRI and computationally modelled tissue parameters to be significantly correlated.

METHODS: Using a clinical 3.0-T system (Philips, Achieva), spatially resolved T1, T1ρ, T2 and T2* maps of intact cartilage samples (n=8) were generated and mean parameter values were calculated in distinct regions-of-interest (ROIs) (Fig. 1a-c). Samples underwent histological evaluation using the Mankin classification to ensure histological integrity (defined as Mankin grade 0) (Fig. 1d). For cross-referencing, a discretized numerical model capturing the distinct compositional and structural tissue properties of cartilage as a function of sample depth, i.e. fluid fraction (FF), proteoglycan (PG) and collagen (CO) content and collagen fiber orientation (CFO), was implemented on the basis of validated literature data (Wilson et al., 2007, BMMB) (Fig. 1e). Pixel-wise and ROI-specific, qMRI parameters and modelled tissue parameters were correlated using Spearman's correlation and quantified by Spearman's correlation coefficient ρ_s (Fig. 1f).

a)

	Quantitative MRI Parameters								Computationally Modeled Parameters			
	Peripheral Region				Central Region				All Regions			
	T1 [ms]	T1ρ [ms]	T2 [ms]	T2* [ms]	T1 [ms]	T1ρ [ms]	T2 [ms]	T2* [ms]	FF [%]	CO [%]	PG [%]	CFO [°]
SZ	682±77	63±53	35±12	29±63	675±94	79±62	35±15	35±53	78±11%	8±1%	14±6%	90±0°
TZ	700±29	52±21	37±12	29±17	701±41	61±26	36±12	32±20	70±9%	9±1%	20±9%	45±32°
DZ	585±6	51±9	27±8	22±5	589±13	58±10	27±7	24±7	51±7%	20±3%	29±11%	0±0°
p-value	**0.017**	0.512	0.08	0.110	**0.042**	0.652	0.183	0.054				



		Quantitative MRI Parameters							
		Peripheral Region				Central Region			
		T1	T1ρ	T2	T2*	T1	T1ρ	T2	T2*
Computationally Modeled Parameters	FF	0.66 (***)	0.16	0.58 (***)	0.55 (*)	0.8 (***)	0.15 (*)	0.71 (***)	0.71 (***)
	CO	-0.65 (***)	-0.15	-0.58 (***)	-0.55 (*)	-0.81 (***)	-0.13 (*)	-0.71 (***)	-0.73 (***)
	PG	-0.66 (***)	-0.16	-0.58 (***)	-0.55 (*)	-0.8 (***)	-0.15 (**)	-0.71 (***)	-0.71 (***)
	CFO	0.5 (***)	0.16 (*)	0.54 (***)	0.44 (**)	0.7 (***)	0.16 (**)	0.69 (***)	0.67 (***)

Fig. 1: a) Mean qMRI parameter [ms] and computationally modeled tissue parameter values [%]. M ± SD. Zonal assessment of superficial, transitional and deep zones (SZ, TZ, DZ) using Kruskal Wallis test (significant differences bold). b) T2-weighted morphological image with segmentation routines and regions-of-interest: central region and peripheral regions (CR, PR); c) Exemplary T2* map and d) corresponding histological section (HE stain). e) Cartilage constituents as a function of normalized depth, adapted from Wilson et al., 2007, BMMB. f) Spearman's correlation coefficients between the modeled and qMRI parameters. Significant correlations bold and stratified as $0.01 < p \leq 0.05$ (*), $0.001 < p \leq 0.01$ (**), and $p \leq 0.001$ (***).

RESULTS: QMRI and computationally modeled parameter data are displayed in Fig. 1a. Significant correlations were found between computationally modeled parameters and T1, T2 and T2*, in particular in the central region (CR: T1: $\rho_s \geq 0.7$ [FF, CFO], $\rho_s \leq -0.8$ [CO, PG]; T2 and T2*: $\rho_s \geq 0.67$ [FF, CFO], $\rho_s \leq -0.71$ [CO, PG]) as compared to the peripheral region (Fig. 1f). For T1ρ, correlations were considerably weaker and fewer (Fig. 1f).

CONCLUSION: QMRI parameters could be further characterized in their diagnostic performance in a basic scientific context. Even though no parameter is specific towards any particular cartilage constituent, T1, T2 and T2* are more reflective of tissue compositional features than T1ρ.

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CARTILAGE AND SUBCHONDRAL BONE ANALYSES ACROSS THE TIBIA IN HUMAN OSTEOARTHRITIC KNEE VERSUS NORMAL KNEE: A MICRO-CT STUDY

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INTRODUCTION: Cartilage, meniscus subchondral plate and trabecular bone represent a functional unit. The destruction of articular cartilage seems to be the main feature of OA, but the local dependence of cartilage and subchondral bone impairments at the microscopic level is not known.

OBJECTIVE: To determine differences in trabecular and subchondral plate bone and cartilage thickness between osteoarthritic (OA) and normal knees in peripheral and central locations of the medial compartment.
METHODS: In 46 cadaveric left knees (26 women and 20 men), the Kellgren-Lawrence (KL) score was determined from post mortem antero-posterior radiographs: KL=0 (n=12), KL=1 (n=21), KL=2 (n=2), KL=3 (n=9) and KL=4 (n=2). 33 knees with KL=0 and KL=1 were considered as controls (n=19 women, n=14 men) and the remaining 13 (n=7 women and n=6 men) were considered as OA. After dissection, 2 vertical cores (7 mm ∅) were extracted in the central region of the medial tibial plateau (S1) not covered by meniscus and a peripheral and lateral location (S2) fully covered by the meniscus. Each core was imaged with micro-CT (SkyScan 1172®; pixel size 10µm). Cartilage thickness (Cart.Th,mm) and subchondral bone plate thickness (SBP_Th,mm) and porosity (SBP_porosity,%) were measured. In the first 5mm beneath the SBP: Bone Volume/Total Volume (BV/TV,%), Trabecular Number (Tb.N,1/mm), Trabecular Thickness (Tb.Th,mm), Trabecular Separation (Tb.Sp,mm), Degree of Anisotropy (DA), Structure Model Index (SMI) were measured. Differences between OA and controls for males and females, were analyzed by T-tests.

RESULTS:

	Central position (S1)		Peripheral position (S2)	
1-5 mm	OA	Control	OA	Control
Males	(n=6)	(n=14)	(n=6)	(n=14)
Age	80.6±7.0	79.6±12.9		
Cart_Th	1.34±0.38	2.20±0.5¥††	1.56±0.40	1.84±0.35
SBP_Th	0.54±0.12	0.61±0.20‡	0.45±0.15	0.42±0.20
SBP_porosity	11.2±6.1	14.3±6.9	16.6±9.6	18.2±8.1
BV/TV(%)	42.6±4.8*†	34.9.±8.5‡	34.8±9.4**	23.2±5.9
Tb.Th(mm)	0.23±0.02††	0.21±0.04‡	0.21±0.02**	0.16±0.03
Tb.N(1/mm)	1.83±0.26*	1.63±0.15‡	1.65±0.32*	1.39±0.16
Tb.Sp(mm)	0.44±0.09*	0.50±0.05†	0.50±0.06	0.55±0.06
SMI	-0.02±1.0	0.04±0.61‡	0.02±1.31	0.85±0.34
DA	1.42±0.08	1.38±0.21†	1.58±0.30*	1.89±0.31
Females	(n=7)	(n=19)	(n=7)	(n=19)
Age	85.7±6.0	86.2±8.3		
Cart_Th	1.94±0.97†	2.14±0.38‡	1.11±0.20¥	1.68±0.20
SBP_Th	0.65±0.12	0.65±0.15‡	0.56±0.20*	0.39±0.15
SBP_porosity	11.0±4.7	12.5±4.9††	16.1±9.6	18.2±8.1
BV/TV(%)	27.6±3.5*††	22.9±6.9††	23.3±4.1**	16.8±6.5
Tb.Th(mm)	0.18±0.02††	0.16±0.02‡	0.16±0.02*	0.14±0.03
Tb.N(1/mm)	1.53±0.09*†	1.36±0.27†	1.41±0.16*	1.18±0.25
Tb.Sp(mm)	0.53±0.04	0.57±0.1	0.53±0.06	0.60±0.10
SMI	0.56±0.40*††	0.94±0.40††	0.96±0.37	1.22±0.42
DA	1.49±0.21†	1.52±0.26††	1.92±0.42	1.92±0.44

Differences between control and OA: *p<0.05, ** p<0.01, ¥ p<0.001
Differences between S1 and S2 locations: †p<0.05, ††p<0.01, ‡ p<0.001

For males and females, age did not differ between OA and controls. Cartilage thickness was lower in OA for S1 in males and for S2 in females. SBP_Th and porosity did not differ between OA and controls except for S2 in females. BV/TV and Tb.N differed significantly for both locations in males and females. Tb.Th differed significantly for S2 in both gender but not for S1. Tb.Sp only differed for S1 in males. DA was significantly different for S2 in males. In the controls almost all parameters differed significantly between S1 and S2 for both genders.
In the OA group BV/TV, Tb.Th significantly differed between S1 and S2 for both genders; Cart.Th, Tb.N, SMI and DA differed in females only.

CONCLUSION: In the controls (females and males) in S2, the location protected by the meniscus Cart_Th, SBP_Th, BV/TV, Tb.Th, and Tb.N were lower and SBP_porosity and Tb.Sp were higher compared to S1 indicating somewhat stronger material at the location not covered by the meniscus (although not all difference were statistically significant). The protective mechanism of the meniscus may results from a better load distribution. In Subjects with OA, Cart_Th was reduced, resulting in higher BV/TV, Tb.Th, Tb.N and lower porosity compared to controls, however the differential protective effect of the meniscus remained.

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DISCLOSURE STATEMENT: none
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PREDICTING TOTAL HIP REPLACEMENT FOR SYMPTOMATIC OSTEOARTHRITIS USING RADIOGRAPHS OR CLINICAL COMPUTED TOMOGRAPHY; A PROSPECTIVE CASE-CONTROL STUDY

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INTRODUCTION: Expert osteoarthritis guidance now advises clinicians not to request imaging when managing patients with hip pain.

OBJECTIVE: To evaluate how well OA features (from a digitally-reconstructed AP radiograph of the pelvis, or from clinical CT) predict total hip replacement (THR), compared with pain symptoms alone.

METHODS: From a prospective nested case-control study of 3133 healthy adults, 74 individuals underwent THR for osteoarthritis approximately 3 years after a baseline assessment comprising hip-specific questions from the WOMAC pain questionnaire and hip computed tomography (CT). Each case destined for THR was matched by age and sex to two control individuals. Mean age was 74±5yrs (range 67-89). Baseline variables were performance-tested using receiver-operating-characteristic curve analysis (AUC): hip pain, osteoarthritis grade (KLG) or minimum JSW (mJSW) from coronal plane reconstructed radiograph or 3D cortical bone thickness. The location and magnitude of bone thickening associated with THR was highlighted using statistical parametric mapping.

RESULTS: Combining hip pain, radiographic osteoarthritis grade and CT gave excellent discrimination of THR (0·90; 0·85,0·95). Conversely, hip pain was a poor to marginal predictor (AUC=0·70; 95%CI 0·62,0·78). The AUC for radiographic KL grade of 2 or above was 0·87 (0·81,0·92), irrespective of hip pain, with single mJSW being a reasonable discriminator (0·80;0·73,0·87). Osteoarthritis was also associated with a CT-defined crescent of femoral head surface bone thickening (Odds Ratio for THR; 5 per SD thicker; 3·2,7·7, 0·85 (0·79, 0·91)). In a typical clinical presentation with hip pain, all of the imaging parameters measured ranged from good to excellent in terms of clinical utility.

CONCLUSION: Imaging unequivocally predicted THR for osteoarthritis, whether or not pain had become apparent. Contrary to current guidance, images of patients with hip pain have good to excellent clinical utility for selecting surgically-relevant presentations. If patients with definite hip pain had definite radiological osteoarthritis, 85% went on to THR within 3 years.

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DISCLOSURE STATEMENT: No relevant disclosures
ACKNOWLEDGEMENT: Stephen Kaptoge and Stephen Sharp for statistical assistance.
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IMAGING BIOMARKER BASED PATIENT STRATIFICATION: INITIAL DATA AND VALIDATION IN FOUR MOST COMMON KNEE ARTHRITIC DISEASES

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BACKGROUND: Biomarker science has advanced to aid in distinguishing between different forms of arthritis: inflammatory arthritides such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA) and OA. Biomarkers are also used to assess disease activity. Diagnostic serum biomarkers such as rheumatoid factor (RF) and cyclic-citrullinated peptide (CCP) and assays of disease activity such as C-reactive protein (CRP), and multi-biomarker assays have utility but lack complete sensitivity and specificity. Increasingly quantitative imaging biomarkers may fill an important gap in disease identification and assessment.

OBJECTIVE: 1) To investigate the association between imaging measures of inflammation in the synovium of the knee joint and systemic levels of CRP in patients with RA, PsA and OA. 2) Investigate how imaging and clinical markers correlate to IL-6 levels from joint fluid in different patient cohorts.

METHODS: 38 patients with a flare of pain in the knee were recruited. 12 were diagnosed with RF positive (+) RA, 6 with RF negative (-) RA, 6 PsA, and 14 OA, according to ACR/EULAR criteria. CRP in blood and IL-6 levels from joint fluid were determined. Patients underwent MRI, including Dynamic Contrast Enhanced (DCE)-MRI exam prior to an ultrasound-guided arthrocentesis. MRI were scored for synovitis [1] and DCE-MRI were quantified using Dynamic Enhanced MRI Quantification (DEMRIQ) method, extracting the volume of enhancing voxels (Nvoxel), Initial Rate of Enhancement (IRE), Maximum Enhancement (ME). Inflammation was quantified as IRExNvoxels and MExNvoxels [2]. Correlation between all clinical scores and all imaging parameters was done using Spearman rho, with significance levels of $p<0.05$.

RESULTS: The imaging markers of perfusion in the synovium of the knee (MExNvoxels and IRExNvoxels) were the only imaging measures, which showed a very high association with CRP in both RF+ RA ($r=0.92$ / 0.97, $p<0.05$) and PsA patients (0.93 / 0.99, $p<0.05$), whereas all other imaging markers of inflammation showed no statistical association with blood levels of CRP in these diseases. We found no association between CRP and any imaging assessed scores of inflammation in either RF- RA or OA. In addition, only RF+ RA patients showed a positive moderate to high association between MExNvoxels and IL-6 ($r=0.66$, $p<0.05$) in the knee joint aspirate.

CONCLUSION: Quantitative imaging and blood biomarkers of inflammation, such as DCE-MRI parameters and CRP, appear to relate differently to each other in the four most common knee arthritic diseases, RF + RA, RF- RA, PsA and OA. DCE-MRI may have specific utility in differentiating these conditions and their disease activity.

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SPONSOR: Novo Nordisk A/S
DISCLOSURE STATEMENT: None
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RADIOGRAPHIC OUTCOMES WERE ASSOCIATED WITH PAIN AND FUNCTION RESPONSES: POST-HOC ANALYSIS FROM A PHASE 2 STUDY OF WNT PATHWAY INHIBITOR, SM04690, FOR KNEE OSTEOARTHRITIS

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INTRODUCTION: SM04690, a small molecule intra-articular (IA) Wnt pathway inhibitor, is in development as a potential disease-modifying osteoarthritis drug (DMOAD). A phase 2, 52-week, randomized controlled trial evaluated changes in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain & Function and medial joint space width (mJSW). It was hypothesized that observed mJSW improvement was associated with increased probability of symptomatic response. To test this hypothesis, a post-hoc concordance analysis was performed between mJSW change and WOMAC Pain & Function responders.

OBJECTIVE: To evaluate concordance between mJSW and WOMAC Pain and Function responders.

METHODS: Subjects with knee OA, Kellgren-Lawrence (KL) grades 2-3, received 2 mL IA SM04690 (0.03, 0.07, or 0.23 mg) or placebo (PBO) in the target (most painful) knee. WOMAC Pain [0-50] and Function [0-170] were assessed at Weeks 0, 4, 13, 26, 39, and 52 and knee radiographs at Weeks 0, 26, and 52. Baseline-adjusted logistic regression group analyses estimated concordance between mJSW change and pain and function changes for responders (defined as achieving both WOMAC Pain and Function improvements of ≥50% and ≥20 [scaled to 100] points). Receiver-operator characteristic (ROC) curves were generated with area under the curve (AUC) to estimate concordance (AUC > 0.7 = 'acceptable' and > 0.8 = 'excellent' concordance). Intention-to-treat (ITT) and two subgroups were analyzed: 1) unilateral symptomatic knee OA (pre-specified; UNI) and 2) unilateral symptomatic knee OA without widespread pain or comorbid symptoms (Widespread Pain Index ≤4 and Symptom Severity ≤2; post-hoc; UNI-WP). 455 subjects were enrolled (mean age 60.3 [±8.7] years, body mass index 29.9 [±4.6] kg/m^2, 268 [58.9%] female, 292 [64.2%] KL grade 3, and 164 [36.0%] UNI).

RESULTS: In ITT, approximately 53% were responders across all groups. In UNI, 20 (56%) 0.03 mg; 20 (63%) 0.07 mg; 23 (64%) 0.23 mg; and 15 (47%) PBO, and in UNI-WP, 15 (56%) 0.03 mg; 16 (62%) 0.07 mg; 19 (70%) 0.23 mg; and 12 (44%) PBO were responders. The 0.03 mg (UNI, P=0.104; UNI-WP, P=0.047) and 0.07 mg (UNI, P=0.009; UNI-WP, P=0.013) doses demonstrated increased mJSW compared with PBO at Week 52. In ITT, no treatment group achieved ROC AUC > 0.7 (Figure). In UNI, the 0.07 mg dose demonstrated 'acceptable' (AUC=0.783), and in UNI-WP, the 0.07 mg dose showed 'excellent' (AUC=0.825) concordance between mJSW change and response.

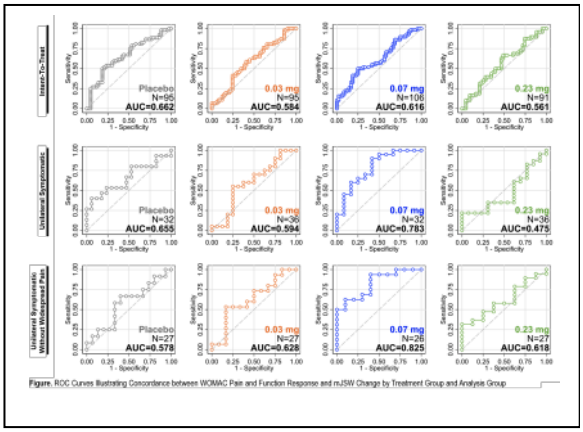

Figure. ROC Curves Illustrating Concordance between WOMAC Pain and Function Response and mJSW Change by Treatment Group and Analysis Group

CONCLUSION: In a post-hoc analysis of UNI and UNI-WP 0.07 mg cohorts, changes in mJSW were concordant with WOMAC Pain and Function responses. Concordance analysis can potentially characterize the strength of relationship between radiographic change and clinical outcomes when investigating potential DMOAD treatments in knee OA.

SPONSOR: Samumed, LLC.
DISCLOSURE STATEMENT: C.J. Swearingen, S. Kennedy, and J.R.S. Tambiah are employees and shareholders of Samumed, LLC. M. Hochberg is a consultant for Bioberica, EMD Serono, Novartis Pharma AG, Plexxikon, Pfizer, Proximagen, Regeneron, Samumed, LLC, and Theralogix, LLC.
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INITIAL STRUCTURAL RESPONSE PREDICTS LONG-TERM SURVIVAL OF KNEE JOINT DISTRACTION AS A TREATMENT FOR KNEE OSTEOARTHRITIS

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INTRODUCTION: In relatively young patients with end-stage knee OA, TKA comes with the risk of future revision surgery. Knee joint distraction (KJD) is a joint preserving surgery technique, which has been shown to provide sustained clinical and structural improvement for at least five years and postpones the need for TKA.

OBJECTIVE: 1) To evaluate long-term clinical and structural results and 2) to identify characteristics predicting survival of the native knee joint after KJD.

METHODS: Tibiofemoral OA patients (n=20; age <60 years) indicated for TKA were treated with KJD. Distraction surgery was performed by use of two external fixators with built in springs, placed lateral and medial of the knee joint. The knee was distracted 5 mm for 6 weeks and weight-bearing was encouraged. WOMAC questionnaires (100 best) and VAS pain scores (0 best) were used for clinical evaluation at baseline and each consecutive year after treatment, up to 9 years. Minimum and mean joint space width (JSW) and mean bone density of the most affected compartment (MAC) were measured using KIDA software on standardized radiographs (baseline and 1, 2, 5 and 7 years after treatment). The mean cartilage thickness of the MAC was measured on MRI scans using the Eckstein protocol (baseline and 1, 2 and 5 years after treatment). Survival after treatment was analyzed (failure defined by TKA). Prediction of KJD survival was studied by logistic regression analyses

RESULTS: Three patients withdrew consent. Nine years after treatment, survival was 48%. Survival percentages differed significantly for gender (women 14%, men 70%; p=0.035) and for increase in minimum JSW in the 1st year (<0.5mm increase 0%, >0.5mm increase 72%; p=0.002).
Survivors reported clinical improvement compared to baseline: ΔWOMAC +29.9 points (95%CI +16.9 to +42.9; p=0.001), ΔVAS -46.8mm (95%CI -31.6 to -61.9; p<0.001). In addition, a significant increase of the minimum JSW (+0.62mm; 95%CI +0.13 to +1.11; p=0.020) was found after seven years. No significant changes were found for the mean JSW (+0.36mm; 95%CI -0.85 to +1.57; p=0.505). In patients whose treatment failed over time, last reported clinical scores were still improved compared to baseline: ΔWOMAC +20.5 points (95%CI -1.8 to +42.8; p=0.067), ΔVAS -25.4mm (95%CI -3.2 to -47.7; p=0.030). In contrast, the minimum JSW (+0.22mm; 95%CI -0.15 to 0.58; p=0.205) and mean JSW (+0.21mm; 95%CI -1.08 to 1.51; p=0.712) at the last reported time points were no longer increased.
Male gender and minimum JSW increase after one year predict survival of the native knee joint after nine years (OR of 14 and 101; both p<0.046). The 1-year bone density decrease and mean cartilage thickness increase had a tendency to be predictive (OR of 0.73 and 170; both p<0.090).

CONCLUSION: Joint distraction for end-stage knee OA shows long-lasting clinical and structural improvement with a survival of 48% at 9 years. Clinical scores in patients failing treatment were still improved compared to baseline and cannot fully explain the subsequent TKA surgery. Positive predicting factors for survival of the native knee are male gender and a larger initial increase in minimum JSW and potentially, an initial decrease in bone density and an increase in mean cartilage thickness are predictive as well. Overall, the initial structural response after KJD appears to be important for long-term success of the treatment.

SPONSOR: Dutch Arthritis Association (project number LLP-9).
DISCLOSURE STATEMENT: FPJG Lafeber is co-founder, co-director, and shareholder of ArthroSave BV, a medical device company involved in marketing a user-friendly knee joint distraction device.
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IMPLEMENTING A NOVEL 3D JOINT SPACE QUANTIFICATION METHOD BY CT IN PATIENTS WITH KNEE OSTEOARTHRITIS

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INTRODUCTION: In knee OA patients, the JSW is commonly measured on weight-bearing radiographs to quantify cartilage thickness loss in OA progression or regeneration after treatments such as knee joint distraction (KJD). Performing measurements on 3D imaging techniques could provide more insight into the JSW distribution throughout the joint, but a validated measuring method has not yet been developed.

OBJECTIVE: 1) To develop an intuitive method of visualization and quantification of the 3D JSW distribution and 2) to compare it to a current gold standard.

METHODS: Standardized (non-weightbearing) CT scans and weight-bearing plain radiographs were performed in 33 knee OA patients, after which 16 of these patients were treated with KJD. Additional CT scans and radiographs were performed one and two years after treatment. The medial and lateral JSW were measured on all plain radiographs as a gold standard using in-house developed KIDA software. A semi-automatic method was developed to measure 3D JSW distances in all CT scans. Heat maps and histograms were generated to provide insight in the joint space distribution, represented by the median medial and lateral JSW. CT and plain radiograph JSW measures were compared cross-sectionally across all patients and time points, and longitudinally for one-year changes in KJD patients, for the medial and lateral compartment and the most affected compartment (MAC).

RESULTS: Heat maps and histograms can display 3D joint space distribution and indicate patient-specific changes over time (figure 1). Cross-sectional correlations were strong for the medial and MAC and moderate for the lateral compartment (Pearson R = 0.78, 0.74 and 0.52 respectively; all $p<0.001$). Longitudinal correlations were weak-moderate and significant only for the MAC (R=0.35; p=0.050). In 63% of the cases, longitudinal KIDA and CT results showed an agreement in change direction (both showing JSW increase or decrease in the MAC).

CONCLUSION: The developed 3D JSW measurement method can quantify and visualize joint space distances and distributions throughout the joint and shows a good cross-sectional correlation with gold standard plain radiography, but a weaker longitudinal correlation. This might be caused by a difference in resilience of degenerated / regenerated cartilage expressed by the weight-bearing differences between the two imaging techniques. Future research into the effect of weight-bearing on the 3D joint space distribution in knee OA patients is currently being performed.

SPONSOR: ZonMw (The Netherlands Organisation for Health Research and Development, project number 95110008)
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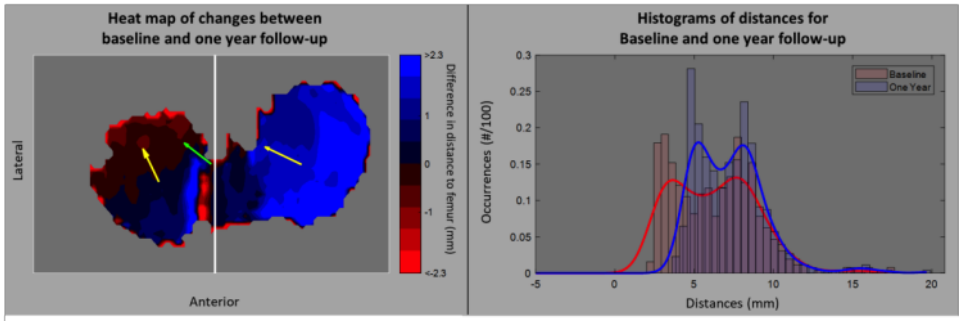

Figure 1 Left: Heat map of differences in distances from the tibia plateau to the femur at one year of follow-up compared to baseline for one patient, where blue indicates a distance increase and red indicates a decrease. The arrows indicate a distance shift in the joint (green arrow for the whole joint, yellow arrows for each side separately), i.e. the joint space decreases lateral-posteriorly and increases in the MAC; medially. Right: Histograms of joint space distance distributions at baseline (red) and one year of follow-up (blue) for the same patient.

HYALURONAN DERIVATIVE HYMOVIS® INCREASES CARTILAGE VOLUME AND TYPI II COLLAGEN TURNOVER IN OSTEOARHRITIC KNEE: DATA FROM MOKHA STUDY

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BACKGROUND: Intra-articular injections of hyaluronan represent one of the well-accepted standard of care for treating symptomatic knee osteoarthritis (OA). Until now, not much is known about the structural-modifying effect of this treatment justifying this pilot study.

METHODS: Forty-six patients with symptomatic knee OA (mean age 61.4 years [min.35-max.80; 67.4% female; Kellgren & Lawrence grade II &nd III (63% and 37%, respectively); mean BMI 30.6 kg/m2] were enrolled in this open-label, prospective, multicenter, pilot study. Patients received two treatment cycles of intra-articular injections (3 mL) of HYMOVIS® (8 mg/mL of hyaluronic acid hexadecylamide at 6 months interval. Each treatment cycle involved two intra-articular injections one week apart. All patients had MRI of the target knee at baseline and 1 year, and blood samples (D30, D90, D180, D210 and D360) to assess joint biomarkers. The primary outcome was the change in type II collagen-specific biomarkers (Coll2-1, Coll2-1NO2 and CTX-II) after HYMOVIS® treatment versus baseline. Secondary endpoints included levels changes in CS-846, COMP, PIIANP, MMP-3, MPO and IL-6 serum biomarkers, the ratio Coll2-1/PIIANP, CTX-II/PIIANP, variation of MRI cartilage volume, and KOOS index.

RESULTS: Coll2-1 serum levels significantly increased overtime ($P<0.001$) while Coll2-1NO2 levels were only increased at D360 ($p<0.05$). Serum PIIANP levels also progressively and significantly enhanced with time ($p<0.001$). In contrast, other serum biomarker levels including CTX-II, AGG, COMP, MMP-3, MPO or IL-6 did not change significantly overtime. Interestingly, the ratios Coll2-1/PIIANP and CTX-II/PIIANP decreased ($p<0.005$), indicating a decrease of cartilage catabolism. Compared to baseline value, MRI cartilage volume and thickness increased in lateral femoral and lateral trochlea compartments ($p<0.05$) and not in medial compartment. These results, in addition to an improvement of T2 mapping score suggest a positive structural effect of the product. Interestingly, WORMS effusion score, an indicator of synovitis, significantly decreased ($p<0.016$). Finally, global KOOS score and subscales significantly increased overtime ($p<0.001$) while pain at rest, walking pain and patients or investigators global assessment of disease activity decreased ($p< 0.001$). The safety profile was favorable with a low incidence of injection-site pain.

CONCLUSION: HYMOVIS®, a well-tolerated intra-articular treatment, significantly enhanced type II collagen turnover as suggested by the increase in Coll2-1 and PIIANP levels and cartilage volume observed by MRI in lateral knee compartment. Importantly, this study highlighted the potential symptomatic benefit of HYMOVIS® on pain and function and provides critical information for the design of a larger phase III clinical trial.

SPONSOR: Fidia Farmaceutici, S.p.A., Abano Terme, Italy
DISCLOSURE STATEMENT: The authors have no conflict of interest
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MAGNETIC RESONANCE IMAGING PARAMETER MAPPING OF *EX VIVO* HUMAN MENISCI

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INTRODUCTION: Meniscal degeneration is associated with knee OA and commonly begins in the medial posterior horn. MRI relaxation parameters, e.g. T1 and T2 are affected by molecular composition and tissue structure and could thus be indicative of tissue degeneration. However, T2 mapping is challenging in the meniscus due to the rapidly decaying signal. This issue may be addressed through the use of ultra-short echo time (UTE) sequences, with which we can measure T2*.

OBJECTIVE: To compare MRI relaxation parameters (T2*, T2, T1) between medial and lateral menisci from knee OA patients, and medial menisci from donors without known knee OA.

METHODS: We used human menisci from a local biobank. Both medial and lateral menisci were sampled from medial compartment OA patients (n=10, 50-75 years old) undergoing total knee replacement. Medial menisci from deceased donors (n=10, 18-77 years old) without known knee OA were also included as references. The posterior horn was cut out and placed in a 50-ml plastic tube filled with phosphate buffered saline. MRI measurements were made in a preclinical 9.4 T scanner, with the sample placed in an orientation similar to the *in vivo* case. For T2* mapping, eight measurements were acquired with a single echo UTE sequence with different TEs (0.5, 1, 2, 4, 6, 8, 10, and 12 ms). T2 mapping was performed with a single echo RARE sequence with TEs of 4.7, 7, 9, 11, 13, 15 and 17 ms. T1 mapping was performed using a RAREVTR sequence with TRs of 6000, 3000, 1500, 800, 400 and 200 ms. Mean T2, T2* and T1 values were calculated within a region of interest (ROI) covering a cross section of the meniscus. Difference in mean with 95 % CI were calculated for pairwise comparisons between meniscus groups using t-tests.

Table 1. Difference in mean for T2*, T2 and T1 with 95 % CI between medial OA, lateral OA and reference menisci (shortened as Med, Lat and Ref) adjusted for age.

	Difference in mean with 95 % CI		
	T2* [ms]	T2 [ms]	T1 [ms]
Med – Ref	4.8 (1.9, 7.8)	4.7 (1.0, 8.5)	200 (77, 310)
Med – Lat	6.1 (2.9, 9.3)	8.4 (5.8, 11)	180 (77, 280)
Lat – Ref	-0.53 (-2.8, 1.7)	-3.0 (-6.1, 0.17)	21 (-45, 86)

RESULTS: Mean values for all three parameters differed significantly between medial menisci from OA patients compared to medial reference menisci and lateral OA menisci (table 1). We also observed tendencies towards higher T2* and T1 values with increasing age for the reference menisci (figure 1).

CONCLUSION: High values of the MRI relaxation parameters T2*, T2 and T1 could be indicative of meniscus degeneration. The lateral meniscus is more similar to medial references than to the medial OA meniscus and could possibly be used as an internal reference in future *in vivo* experiments. Within the reference group, there are tendencies towards increasing relaxation values with age, suggesting that age-related processes occur in the meniscus.

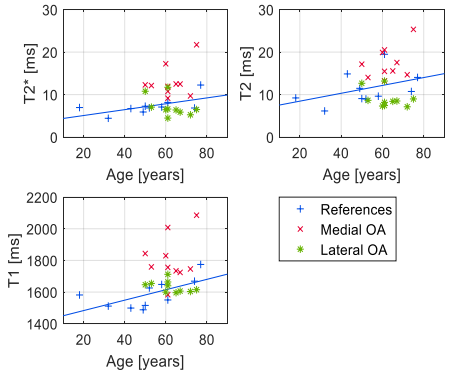

Figure 1 Mean values of T2*, T2 and T1 for each meniscus vs. age. Blue line represents linear regression for reference menisci.

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QUANTIFYING TOTAL BURDEN OF KNEE OA USING SEMI-QUANTITATIVE KNEE MRI ASSESSMENT

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INTRODUCTION: Semi-quantitative (SQ) assessment of MRI has been shown to be a valid and reliable way to measure knee OA structural severity. SQ scoring systems rely on the ordinal grading of knee features evaluated across multiple intraarticular subregions. There are few studies on how to best combine these ratings to define the most robust measure of structural disease severity.

OBJECTIVE: To use comprehensive statistical analysis to determine how to best utilize MRI Osteoarthritis Knee Score (MOAKS) assessments to quantify the burden of osteophytes in knee OA.

METHODS: We used data from the OAI FNIH OA Biomarkers Consortium case-control study. 194 cases were knees with both JSN and pain progression over 48 months of follow-up. 406 controls were all other knees. Baseline MRIs were read according to MOAKS. Here we focus on osteophyte size, scored in each of 12 locations. We used a mixed-effects location-scale model to simultaneously analyze osteophyte size score in each location to assess whether cases and controls differ with respect to 1) the average score across all 12 locations; 2) the variability across locations. To illustrate these results, we created groups based on osteophyte score using two approaches: 1) categorizes participants based on tertiles of osteophyte score (summed across all 12 locations); 2) additionally incorporates number of locations affected. We used a logistic regression model to evaluate the association between case status and osteophyte group.

RESULTS: Location-scale models demonstrated that both the mean location score and the within-subject variability of the location scores are statistically significantly associated with case status. Using score categories, the first approach based only on summed total score showed a dose-response relationship between total score and the odds of being a case (Table). The second approach (incorporating number of subregions) showed that subjects with a more sub-regions affected (i.e., many smaller osteophytes) had higher odds of being a case compared to those with fewer sub-regions affected (i.e., fewer larger osteophytes) (Table).

CONCLUSIONS: Both the summed amount of joint damage and the number of subregions affected are important in the interpretation SQ assessments of knee MRI in knee OA. Researchers should consider a summary variable that encompasses both total sum and variability in MOAKS scores. Future work will consider how the pattern of burden is associated with patient-reported outcomes such as pain and function.

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Table. Results of logistic regression: OR (95% CI) of being a case by osteophyte burden.

Approach 1		Approach 2		
Total Score	OR (95% CI)	Total Score	Locations affected	OR (95% CI)
Low	REF	Low		REF
Moderate	1.8 (1.1, 2.7)	Moderate	Fewer	1.3 (0.7, 2.5)
		Moderate	More	2.1 (1.2, 3.4)
High	2.3 (1.5, 3.5)	High	Fewer	0.9 (0.4, 2.0)
		High	More	2.9 (1.8, 4.4)

CROSS SECTIONAL AND LONGTIUDIINAL THIGH MUSCLE AND ADIPOSE TISSUE STATUS IN PERSONS WITH UNILATERAL RADIOGRAPHIC KNEE OSTEOARTHRITIS - DATA FROM THE OSTEOARTHRITIS INITIATIVE

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INTRODUCTION: Previous studies reported inconclusive results whether thigh muscles strength and thigh muscle and adipose tissue cross-sectional areas are associated with radiographic knee osteoarthritis (RKOA) [1-4]. However, knowledge on the association between thigh muscle and adipose tissue status and RKOA is important, as muscle thigh and adipose tissue status are potentially modifiable risk factors.

OBJECTIVE: To compare thigh muscle and adipose tissue anatomical cross sectional areas (ACSAs) cross-sectionally and longitudinally between both limbs of OAI participants with unilateral RKOA in a within-person study design eliminating potential between-subject confounding factors (e.g., BMI, height).

METHODS: 150 female participants (age=65.2 years, BMI=27.3 kg/m²) from the Osteoarthritis Initiative (OAI) with baseline Kellgren Lawrence grade (KLG) KLG=0 in one and KLG≥2 in the contralateral knee, but without a trauma history in that CL knee, were included in the study. Axial T1-weighted spin echo thigh MRIs acquired at 33% of the femoral length (from distal to proximal) were analyzed at year 2 (Y2) and year 4 (Y4) follow-up, with the analysis currently completed for 58 participants. Extensor and flexor ACSAs and adipose tissue (subcutaneous fat [SCF] and intermuscular fat [IMF]) were determined using Active Shape Model based segmentation. ACSA status at Y2, and longitudinal change between Y2 and Y4, were compared between both limbs of the same person, using a paired t-test.

RESULTS: At Y2, no statistically significant differences in thigh muscle status (extensor and flexor ACSAs) or adipose tissue status (SCF and IMF) were observed between both sides (Table 1). Further, no statistically significant differences were observed in longitudinal change (Y2 to Y4) in flexor ACSAs or adipose tissue ACSAs (SCF and IMF, Table 2). A trend for greater extensor ACSAs loss was observed for the RKOA limbs (-0.9±2.6 cm^3) vs the non-RKOA limbs (-0.4±2.4 cm^3), but the differences did not reach statistically significance (p=0.060, Table 2).

Table 1: Year 2: Thigh muscle and adipose tissue ACSAs [cm3] in RKOA vs non-RKOA limbs

	Quadriceps	Hamstrings	Subcutaneous Fat	Intermuscular Fat
KLG = 0	39.3±8.0	25.5±5.1	88.7±33.5	12.3±4.0
KLG ≥ 2	38.7±8.1	26.0±5.0	89.2±32.3	12.5±4.3
P-Value	0.298	0.075	0.588	0.378

Table 2: Year 2→Year 4: Thigh muscle and adipose tissue ACSAs [cm3] in RKOA vs non-RKOA limbs

	Quadriceps	Hamstrings	Subcutaneous Fat	Intermuscular Fat
KLG = 0	-0.4±2.4	-0.4±1.9	-0.9±11.7	-0.1±4.0
KLG ≥ 2	-0.9±2.6	-0.3±1.8	-1.8±10.2	0.1±1.5
P-Value	0.060	0.883	0.169	0.559

CONCULSION: Using part of the available sample, thigh muscle and adipose tissue ACSAs at Y2 and the change between Y2 and Y4 were not found to differ statistically between knees with vs without radiographic KOA in this within-person study design. Longitudinal change of the quadriceps, however, was suggestive of a greater decline in OA than KLG0 knees. Given the limited sample size, these findings will have to be confirmed in the full sample of 150 OAI participants with primary, unilateral knee OA.

REFERENCES: [1] Ruhdorfer et al. Arthritis Care Res (2014), [2] Ruhdorfer et al. Osteoarthritis Cartilage (2014), [3] Culvenor et al. Arthritis Care Res (2017), [4] Kemnitz et al. Osteoarthritis Cartilage (2017)

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DICLOSURE STATEMENT: Chondrometrics GmbH (J. Kemnitz, F. Eckstein, W. Wirth)
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DISEASE MODIFYING EFFECTS OF THE CANINE IL4-10 FUSION PROTEIN IN THE CANINE GROOVE MODEL OF OSTEOARTHRITIS

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OBJECTIVE: An ideal disease modifying osteoarthritis (OA) drug should have analgesic, chondroprotective and anti-inflammatory effects. A fusion protein of Interleukin 4 and 10 (IL4-10FP) might have these effects, as shown in previous studies. Repeated intra-articular injection of human IL4-10FP led to antibody formation in the canine Groove model, neutralizing its effects and inducing inflammation. This study evaluates the effects of species specific canine IL4-10FP (cIL4-10FP) in the canine Groove model of OA.

METHODS: In 8 skeletally mature dogs, knee OA in the right leg was induced according to the Groove model. After 6 weeks, intra-articular injections in the affected knee with either PBS (500µl; n=4) or cIL4-10FP (10µg/500µl; n=4) were given for 10 weeks (1/week).
Force plate analysis (FPA) was used to determine vertical peak force (Fz), braking force (Fy+) and propulsive force (Fy-) in order to evaluate pain. Ratios of right to left hind leg were calculated per dog. FPA was performed before Groove surgery to determine baseline values, and before and after 1st, 6th and 9th intra-articular injection. A linear mixed model was used to evaluate effects of injections 24h after injections. After 10 weeks dogs were euthanized and tissue samples were harvested. Antibody formation against cIL-410FP was evaluated by Immunoglobulin G (IgGs) titers in serum of cIL4-10FP treated dogs. Cartilage proteoglycan content and release of proteoglycans were determined *ex vivo* by Alcian Blue assay. Left knees served as controls. Synovial inflammation was evaluated by HE-staining.

RESULTS: After OA induction a clear reduction in Fz and Fy+ was found. After treatment Fz and Fy+ were increased in the cIL4-10FP group compared to the PBS group (p=0.002 and p=0.01, resp.). Fy- showed a similar pattern although not statistically significant.
No IgGs were detected after 10 injections. Compared to contralateral controls, proteoglycan content of OA PBS injected suggested tissue degeneration (34 *vs.* 27 mg/g). In the cIL4-10FP group proteoglycan content in right knees was not different to contralateral controls (33mg/g vs 31mg/g). Moreover, mean change in proteoglycan content was higher in the cIL4-10FP group compared to the PBS group (4mg/g vs -7mg/g; p=0.057). A similar pattern was found for change in release of proteoglycans, which was statistically significant less increased in the cIL4-10FP group compared to the PBS group (0.4% vs 3.0%; p=0.029). Synovial inflammation was mild (characteristic of this model) and did not change after intra-articular injections (0.4 and -1.3 out of 18 for cIL4-10FP and PBS resp.).

CONCLUSION: Repetitive intra-articular injection with cIL4-10FP did not lead to antibody formation. Dogs treated with cIL4-10FP showed improved loading of the affected joint as compared to PBS treated dogs, reflecting an analgesic effect. Furthermore, improved proteoglycan content and release in cIL4-10FP treated dogs indicate a chondroprotective effect, confirming human in vitro experiments. In both groups, limited synovial inflammation could be detected, being characteristic for the Groove model. These results clearly warrant further research to develop IL4-10FP as a DMOAD.

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IL4-10 FUSION PROTEIN HAS CHONDROPROTECTIVE, ANTI-INFLAMMATORY AND ANALGESIC EFFECTS IN THE TREATMENT OF OSTEOARTHRITIS

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OBJECTIVE: An effective DMOAD should preferably have chondroprotective, anti-inflammatory, and analgesic activity combined in a single molecule. We developed a fusion protein of IL4 and IL10 (IL4-10-FP), in which the biological activity of both cytokines is preserved. The present study evaluates the chondroprotective, anti-inflammatory, and analgesic activity of IL4-10-FP in *in vitro* and *in vivo* models of osteoarthritis.

METHODS: Human osteoarthritic cartilage tissue and synovial tissue were cultured with IL4-10-FP. Cartilage proteoglycan turnover and release of pro-inflammatory, catabolic, and pain mediators by cartilage and synovial tissue were measured. The analgesic effect of intra-articular injected IL4-10 FP was evaluated in a canine OA model by force-plate analysis.

RESULTS: Proteoglycan **(**PG) synthesis in OA cartilage samples was increased in the presence of IL4-10-FP by 45% (p=0.018) while the PG release measured by release of GAGs was reduced by 11% (p=0.018). Furthermore, IL4-10-FP reduced the release of the inflammatory cytokines IL6 and IL8 of OA cartilage samples (84% and 76%, respectively, both p=0.018) and OA synovial tissue samples (68% and 81%, respectively, both p=0.028). The release of MMP3 by osteoarthritic cartilage and synovial tissue was decreased by 39% and 76% respectively (p=0.018 and 0.028) whereas TIMP1 production remained stable. In addition, IL4-10-FP protected cartilage against destructive properties of OA synovial tissue mediators shown by the increased cartilage proteoglycan synthesis (33%, p=0.036) and reduced proteoglycan release (20%, p=0.043). Finally, intra-articular injection of IL4-10-FP improved the deficient joint loading in dogs with experimentally induced osteoarthritis.

CONCLUSION: IL4-10-FP has DMOAD potentials since it shows chondroprotective and anti-inflammatory effects *in vitro*, as well as an analgesic effect in a canine *in vivo* model of osteoarthritis. Further study on its therapeutic potential in osteoarthritis is warranted.

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RESPONSIVENESS OF STANDING CT FOR MEASUREMENT OF KNEE JOINT SPACE NARROWING OVER 60 MONTHS

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INTRODUCTION: Joint space width (JSW) measured on weight-bearing radiographs suffers from poor sensitivity in detection of knee OA as well as poor correlation with symptom progression. Limitations of 2D radiographic JSW, such as the dependence on x-ray beam alignment with the medial tibial plateau, in combination with the temporal and spatial heterogeneity of structural progression of knee OA, limits the responsiveness of radiographic JSW to disease progression. Recent studies examining the responsiveness of radiographic JSN over 3 years report standardized response means (SRM) ranging from -0.03 to -0.74. In contrast, quantitative cartilage thickness on 3D MRI has greater responsiveness to disease progression, with SRM as high as -0.84 over 1 year. However, MRI generally is non-weight-bearing, which may hinder responsiveness due to cartilage swelling and altered position of the menisci. 3D JSW measured on standing CT (SCT) images holds potential to overcome these limitations and enhance responsiveness through measuring JSW in a loaded position, while avoiding bony overlap and error due to beam angle.

OBJECTIVE: To provide preliminary data for the responsiveness of 3D JSW on SCT over 60 months.

METHODS: SCT images of the knee were collected using a commercial scanner (PedCAT, CurveBeam, Warrington, PA) with participants standing in a fixed-flexed configuration. The scanner produced pulsed cone-beam x-ray on a 30×30 cm amorphous silicon flat-panel detector over a 360° projection angle, with a total scan time of 32 seconds (effective radiation dose 0.1 mSv). A 3D dataset with an isotropic resolution of 0.37mm and field of view of 350mm was reconstructed from initial cone beam projections. Tibiofemoral geometries were obtained through semi-automated segmentation of the SCT images as triangulated 3D surface meshes (Seg3D Version 2.4.0). The meshes were minimally smoothed to remove voxellation artifact using Geomagic Design X (3D systems). The 3D JSW was then defined by the Euclidean distance from the center of each triangulated face to the opposing surface along its normal direction. 3D JSW was calculated for 33 knees from 19 participants' at the 84-month visit of the Multicenter Osteoarthritis Study (MOST). At the time of this study, 13 of the 19 participants had returned for the 144-month MOST visit. Of the 23/26 knees available (3 did not have 84-month JSW data), 3D JSW was calculated for 14 knees (1 TKA, 3 knees with absence of joint space, 5 knees with motion artifact) from 11 participants (7 men, mean±SD BMI 29.6±4.3 kg/m^2). The standardized response means (mean change/SD change) were calculated to assess the responsiveness of 3D JSW over 60 months.

RESULTS:

Table 1: Mean Change and Responsiveness to Change in 3D JSW over 60 months.

Threshold	Mean Difference	Standard Deviation	SRM
% Joint Area with JSW<2.0mm on SCT	-3.32%	4.14%	-0.80
% Joint Area with JSW<2.5mm on SCT	-3.31%	3.97%	-0.83

CONCLUSION: These preliminary data support the hypothesis that 3D JSW has greater responsiveness to 60-month change in JSW than has been reported for radiographic JSW over 36-months and similar to that for quantitative cartilage thickness measured on MRI over 12-months. Longitudinal study of the SRM for change in 3D JSW over 24 months is currently underway. Assessing responsiveness by sub-groups (e.g. baseline KLG) and determining the extent to which change in 3D JSW corresponds with changes in knee symptoms will add clinical value.

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ARE MENISCUS POSITION AND MORPHOLOGY ASSOCIATED WITH FAST PROGRESSION IN KNEES WITH EARLY BASELINE RADIOGRAPHIC OA (KLG1)? - DATA FROM THE OAI

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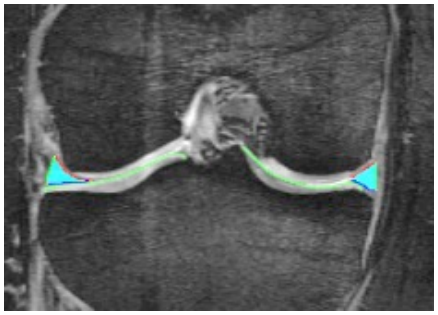
INTRODUCTION: To test disease- (or structure-) modifying drugs (D/SMOADS) at an early stage of knee OA within the practical timelines of a clinical trial, biomarkers enabling the identification of patients at risk of fast progression from an early to an advanced stage of the disease are needed. To this end we studied knees with early baseline signs of radiographic change (KLG1) with incident advanced radiographic disease (i.e. OARSI JSN grade 2 or 3) up to 4-year follow-up (cases). These were compared with matched control knees that maintained KLG1 status throughout 4-years of follow-up.

OBJECTIVE: 1) To determine MRI-based cartilage thickness loss in KLG1 case vs. control knees over 4 years, and 2) to compare characteristics in meniscus position and morphology at baseline, at year-1, and for change from baseline to year-1 follow-up between case and control knees.

METHODS: Baseline KLG 1 status (with central KLG readings present also at year 1 and 4) was observed in 1259 knees (from 1026 of 4796 OAI participants). Of these, 73 knees (from 73 participants) had incident OARSI JSN grade 2 or 3 (KLG 3 or 4) over 4 years; 56 medially, and 17 laterally. Of these 68 knees from 68 participants had longitudinal MRI and clinical data and could be matched 1:1 to a control based on baseline age (±5y.), BMI (±5), WOMAC pain (±5), medial or lateral JSN grade 0 or 1, sex, and side (right, left). Cartilage thickness and meniscus position and morphology were determined from DESS MRIs as described previously [1, 2], the meniscus in 5 central coronally reconstructed 1.5 mm slices (Figure).



RESULTS: In the 68 cases (62% female; age 62.4±8.2 y; BMI of 29.6±4.2), the longitudinal mean cartilage thickness change over 4 years in the medial / lateral femorotibial compartment was substantial (-538±548 / -164±270 µm) and significantly exceeded that in control knees (-12±115 / -24±99 µm, respectively; $p<0.001$; paired t-test). No statistically significant differences were observed in baseline medial meniscus position (e.g. tibial coverage, meniscus extrusion area and distance) or morphology (e.g. height, width or volume). Lateral meniscus measures tended to have more tibial coverage and greater meniscus width in cases than in controls ($p<0.05$ without adjustment for multiple comparisons) at baseline, but the difference became less at year-1 follow-up. Between baseline and year-1, meniscus coverage of the medial tibial plateau decreased by -3mm^2 (-1.6%; [95% CI -4.5, -1.6mm]) in cases vs. -1.2 mm^2 (-0.6%; [95% CI -2.0, -0.3mm]) in controls ($p=0.03$); so did the overlap distance between meniscus and tibial cartilage ($p= 0.02$). The mean extrusion distance increased more strongly ($p=0.01$) in case (0.4mm [95% CI: 0.2; 0.6]) vs. control knees (0.1 mm [95% CI: 0.0; 0.2]) and so did the extrusion area ($p=0.01$). No significant differences in longitudinal change of medial or lateral meniscus position or morphology were observed between case and control knees between baseline and year 1.

CONCLUSIONS: KLG1 knees with incident OARSI JSN grade 2 or 3 over 4 years displayed substantially greater cartilage loss than those that maintained KLG1 status, but no baseline differences in medial meniscus position or morphology were observed between case and control knees. Hence, quantitative measures of baseline meniscus position or morphology did not appear to be associated with subsequent structural progression in knees with baseline KLG 1 and to enable identification of fast progressors. However, greater reduction of tibial coverage by the medial meniscus and greater meniscus extrusion were observed concurrent with severe cartilage loss and incident JSN.

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3D TEXTURE ANALYSIS OF CLINICAL CONE-BEAM COMPUTED TOMOGRAPHY IMAGES REVEALS MICROSTRUCTURAL CHANGES IN OSTEOARTHRITIC HUMAN TRABECULAR BONE

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INTRODUCTION: OA-related bone remodeling affects to the structure of subchondral trabecular bone. These alterations can be quantified in 3D with high-resolution µCT morphometric analysis ex vivo. However, the spatial resolution of clinical cone-beam computed tomography (CBCT) is not adequate for direct quantification of micro-structural trabecular bone morphometrics. In principle, modern texture analysis methods could have a potential to indirectly capture subchondral bone remodeling with CBCT.

OBJECTIVE: To investigate whether OA-related subchondral bone remodeling features can be indirectly quantified from clinical CBCT data using the texture-based, 3D gray-level co-occurrence (GLCM) analysis.

METHODS: Osteochondral cores (n=53, Ø=4mm, ethics approval PPSHP 78/2013, PSSHP 58/2013 & 134/2015) from 9 TKA patients and 2 cadavers were imaged with µCT (Bruker Skyscan 1272; 50kV, 200µA, 2.75µm voxel size, 1200 projections, 0.5mm Al filter) and with CBCT (Planmed Verity; 80kV, 12mA, 200µm voxel size, 300 projections). OA severity of the samples was evaluated with OARSI histopathological grading. Datasets were co-registered, a cylindrical volume-of-interest was selected and trabecular bone was segmented. From the µCT data the BV/TV, Tb.Th, fractal dimension, Tb.Sp, Tb.N, and structure model index (SMI) were calculated. From the CBCT, a rotationally invariant 3D GLCM was calculated through the stacks. Subsequently, the Haralick feature, i.e. GLCM correlation (GLCMcor, parameter which describes the local correlation of the neighboring grey-level values), was calculated.

RESULTS: GLCMcor increased with BV/TV (R=0.782, p<0.001), Tb.Th (R=0.522, p<0.001), Tb.N (R=0.776, p<0.001), fractal dimension (R=0.759, p<0.001), and decreased with Tb.Sp (R=-0.751, p<0.001) and SMI (R=-0.568, p<0.001). Furthermore, statistically significant relationship was found between GLCMcor and OARSI grade (ρ=0.485, p<0.001).

CONCLUSION: GLCM-based texture parameters from clinical CBCT were strongly associated with µCT parameters. Highest correlations of BV/TV, Tb.N, fractal dimension and Tb.Sp. indicate that the GLCMcor is primarily associated with trabecular bone sclerosis. The relationship with GLCMcor and SMI is most likely secondary since SMI is related both with the excess bone formation and the severity of OA. Our results indicate that the 3D GLCM-based texture analysis of clinical CBCT images can be used to indirectly quantify OA-related microstructural trabecular bone alterations.

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DISCLOSURE STATEMENT: None
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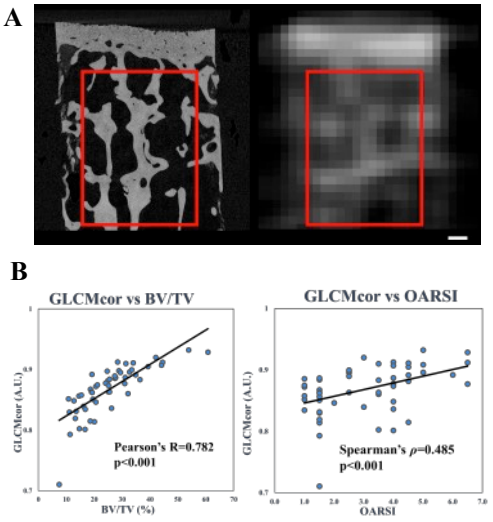

Figure 1. A. Coronal two-dimensional slices from µCT and clinical CBCT datasets. ROI is shown with red rectangle. Scale bar length: 500µm. B. Linear correlation analysis between GLCMcor and BV/TV or OARSI.

IS THE HYPERTROPHIC PHENOTYPE OF TIBIOFEMORAL OSTEOARTHRITIS ASSOCIATED WITH SLOWER PROGRESSION OF DISEASE? THE MOST STUDY

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INTRODUCTION: The hypertrophic phenotype of knee osteoarthritis (OA) refers to joints or compartments exhibiting large osteophytes without severe joint space narrowing (JSN) on radiographs or severe cartilage loss on MRI. This pattern or phenotype, characterized by only mild cartilage loss despite large osteophyte formation is suggestive of more long-standing disease and may potentially be protective against progression of disease when compared to other, non-hypertrophic phenotypes of OA.

OBJECTIVE: 1- To assess the differences in frequencies of any, slow, and slow and fast progression of radiographic JSN and MRI cartilage loss in the tibiofemoral compartments when comparing hypertrophic vs. all other available knees, i.e. exhibiting non-hypertrophic phenotype of OA at baseline; 2- To assess the associations of the presence of hypertrophic tibiofemoral OA at baseline with slow and fast progression of radiographic JSN and MRI cartilage loss using the non-hypertrophic phenotype as the reference standard.

METHODS: We included participants from the Multicenter Osteoarthritis (MOST) Study with available OARSI scores of radiographic JSN and osteophytes and MRI WORMS scores for cartilage morphology, osteophytes, meniscal morphology, and meniscal extrusion, at both baseline and 30 months follow-up. Based on radiographs, hypertrophic tibiofemoral OA was defined as OARSI JSN grades 0 or 1 in both compartments, with one or more osteophytes of grade 3, or 2 or more osteophytes grade ≥ 2. Based on MRI, hypertrophic tibiofemoral OA was defined as large osteophytes (WORMS grades 5-7) in at least one of 10 tibiofemoral subregions but without severe cartilage loss (none of the 10 subregions exhibiting WORMS grades > 3). For both radiographic- and MRI-based hypertrophic OA, non-hypertrophic controls were defined as all other knees with KL grades ≥2 not fulfilling that definition. Progression of radiographic JSN and MRI cartilage loss (from baseline to follow-up) was categorized as (1) no, (2) slow (compartments with a maximum increase of OARSI within-grade change in at least 1 tibiofemoral compartment or an increase up to one WORMS score - including within-grade increase - in at least one of 5 sub regions in the same tibiofemoral compartment between baseline and 30 months), and (3) fast progression (compartments with an increase of OARSI ≥ on full grade in at least one tibiofemoral compartment or an increase of ≥2 grades in at least two of the 5 regions in the same tibiofemoral compartment between baseline and 30 months). Co-variance and logistic regression analyses with generalized estimated equations were performed to assess the associations of hypertrophic OA with any progression, particularly with fast progression, compared with non-hypertrophic OA knees. Results were further adjusted for age, gender, BMI, progression of meniscal pathology, and tibiofemoral malalignment.

RESULTS: 367 knees were included using the radiographic definition (28 hypertrophic OA knees – 7.6%) and 157 knees using the MRI definition (29 hypertrophic OA knees – 18.5%) (1 knee per subject). Using the radiographic definition, more hypertrophic OA knees exhibited fast progression of JSN overtime (28.5% vs. 13.9%) whereas more non-hypertrophic OA knees exhibited slow progression of JSN (16.8% vs. 3.6%), p=0.04. Furthermore, using the radiographic definition, hypertrophic OA was associated with a greater risk for fast progression of JSN when compared to the non-hypertrophic OA phenotype (OR 2.5, 95%CI 1.04, 5.97; p=0.04). However, after adjustment for covariates the relationship was no longer statistically significant (OR 1.9, 95%CI 0.76, 4.98; p=0.17). For the remaining definitions of phenotypes and progression used, no significant relationships were found.

CONCLUSION: Contrary to our expectations, the hypertrophic tibiofemoral OA phenotype is likely associated with faster progression of radiographic JSN when using the radiographic definition, in comparison to all other knees combined, i.e. exhibiting a non-hypertrophic OA phenotype. Missing statistical significance after adjustment or for MRI-defined progression may be due to limited numbers. Summarizing and confirmatory to previous reports, the hypertrophic phenotype seems to be rare.

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DEVELOPMENTAL ORIGINS OF OA: 16-YEAR LONGITUDINAL STUDY EXPLORING ASSOCIATIONS BETWEEN OA KNEE PAIN IN EARLY ADULTHOOD AND BODY COMPOSITION DEVELOPMENT FROM ADOLESCENCE TO ADULTHOOD

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INTRODUCTION: OA manifests in older age but it has been hypothesized that OA has developmental origins similar to osteoporosis or other chronic diseases. Reported associations between body weight at birth or infancy and radiologic or clinical OA presence in later life support this hypothesis. However, no studies have yet assessed if body weight or body composition development during and/or from adolescence to adulthood are associated with early indicators of OA, such as knee pain in early adulthood.

OBJECTIVE: To explore associations between OA knee pain in early adulthood and birth weight, body weight and body composition in adolescent and early adulthood, as well as changes in weight and body composition from adolescence to early adulthood.

METHODS: We used the 'Knee injury and Osteoarthritis Outcome Score' (KOOS) to record knee pain in 50 (30 females) participants (mean age 36.3, SD 2.3 years) of the Saskatchewan Pediatric Bone Mineral Accrual Study (PBMAS). PBMAS is a longitudinal study including serial measures of body composition measures between 8 and 40 years of age We explored relationships between adult KOOS pain score (higher score indicates lower pain) and body weights (recorded at birth and measured in adolescence at the time of the adolescent growth spurt (peak height velocity) and early adulthood) in addition to DXA-imaged total body and trunk fat mass and related changes in weight, total body and trunk fat mass between adolescence and young adulthood using Spearman's rank correlation (ρ).

RESULTS: KOOS pain score (mean=66.6, ranging from 19.4 to 75) was negatively associated with adult weight, total fat mass and trunk fat mass, as well as changes in weight, total and trunk fat mass from adolescence to adulthood with ρ ranging from -0.36 to -0.52 ($p<0.05$). There were no associations between adult knee pain score and birth weight, weight or body fat measured in the adolescence.

CONCLUSION: Knee pain in young adulthood was positively associated with current body weight and fat mass as well as gain in weight and fat mass from adolescence to early adulthood. Together with the observed lack of associations between adult pain score and birth weight, adolescent weight or fat mass, these findings suggest that developmental origins of OA may relate to gains in weight and fat mass from adolescence to early adulthood.

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BONE LOSS IS OBSERVED ALREADY TWO WEEKS AFTER ANTERIOR CRUCIATE LIGAMENT TRANSECTION IN A RABBIT MODEL OF POST-TRAUMATIC OSTEOARTHRITIS

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INTRODUCTION: Subchondral bone sclerosis is a well-known hallmark of OA. Bone loss has been also observed in various OA animal models and also we have previously reported bone loss in the medial femoral condyle in a rabbit model of post-traumatic OA four weeks after ACL transection (ACLT).

OBJECTIVE: This study was aimed at evaluating changes in subchondral plate and trabecular bone morphology in a rabbit model of post-traumatic osteoarthritis two and eight weeks after ACLT surgery.

METHODS: Rabbits were operated for unilateral ACLT. Two and eight weeks (2w and 8w) after surgery, both the operated and contralateral (CL) knees (2w N=8 and 8w N=6) were harvested. Knees from age-matched non-noperated healthy control rabbits served as controls (2w N=8 and 8w N=4). Osteochondral samples were prepared by dissecting knees from 6 compartments – medial femur, lateral femur, medial tibia, lateral tibia, patellofemoral groove (groove) and patella. These samples (n=301) were imaged with μCT (Bruker Skyscan 1272) using 25μm voxel size. Morphological parameters were assessed separately for both trabecular bone and subchondral plate. The trabecular bone volume of interest (Tb.VOI) was generated by manual segmentation. Subsequently, an anisotropic diffusion filter was applied to images followed by global thresholding for bone segmentation. Finally, bone volume fraction (BV/TV), number (Tb.N), thickness (Tb.Th) and separation (Tb.Sp) were assessed for trabecular bone. A subchondral plate mask was generated by subtracting the Tb.VOI from image stack and inverting the Tb.VOI, which was refined by applying 3D shrink-wrap. For subchondral plate we evaluated plate porosity and thickness (Ct.Th). Morphological parameters between groups were evaluated by using Mann-Whitney testing.

RESULTS: Compared with CL knees BV/TV and Tb.Th of operated knees were decreased in the lateral femur (5%, $p<0.05$) and groove (11% $p<0.05$) 2w after surgery. Trabecular bone loss became even more evident 8w after surgery. Compared with controls BV/TV of operated knees was decreased in the lateral femur (14% $p<0.05$), lateral tibia (25% $p<0.0001$), medial tibia (21% $p<0.05$) and groove (28%, $p<0.001$). Compared with the controls, the operated lateral and medial tibia showed decreased Tb.Th by 25% ($p<0.05$) and 16% ($p<0.001$), respectively while Tb.Sp was increased in the medial tibia by 30% ($p<0.05$). Compared with CL, all locations in the operated knees except for the patella showed decreased BV/TV and decreased Tb.Th 8w after surgery. Ct.Th was decreased by 19% in the groove and patella 8w after surgery, when comparing operated knees to CL knees. When comparing operated knees with controls, only the patella showed decreased Ct.Th (23%, $p<0.05$). The groove had increased subchondral plate porosity 8w after surgery when compared either with control (5%, $p<0.01$) or CL knees (6%, $p<0.001$). Finally, plate porosity was increased in the medial femur when compared with controls (4%, $p<0.05$) and in the lateral tibia when compared with CL knees (12%, $p<0.01$).

CONCLUSION: Our post-traumatic OA rabbit model showed surprisingly early trabecular bone loss in the lateral femoral condyle and groove. Loss of the trabecular bone was progressive and became even more evident 8w after surgery. Most likely due to higher metabolic activity of trabecular bone. Subchondral plate thickness was decreased and plate porosity increased in the patella and groove. Our results indicate that bone loss in post-traumatic OA occurs fast and is location-specific. The bone loss is partly related to altered loading as indicated by the differences between operated knees with either controls or CL knees.

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EXPLORING THE SHAPE OF OSTEOARTHRITIS – WITH DATE FROM THE OAI

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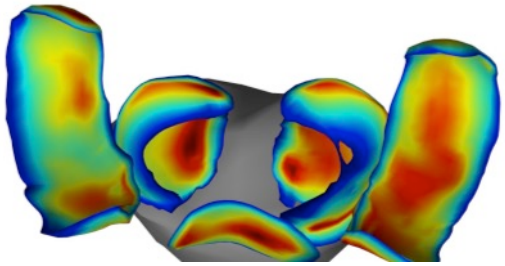
PURPOSE: The role of joint shape in OA has been investigated with a focus on the bones. With large cohorts it is possible to perform shape statistics including bones, cartilages, and menisci and to investigate the relationship between multi-tissue joint shape and OA features.

METHODS: We analyzed the baseline MRIs from the right knees in Osteoarthritis Initiative (OAI). Segmentation and shape was performed using the Knee Imaging Quantification framework (KIQ) resulting in a multi-tissue shape model containing approximately 10,000 3D coordinates for each of the 4695 analyzed MRIs. Principal component analysis followed by partial least squares regression was performed to investigate how much of the variation in a number of OA-related features that could be described by the shape. The Pearson linear regression coefficient r was used to estimate to which to degree the shape described the variation in each feature (as r^2 in %). The number of subjects included varied by the available readings for each feature (n).

RESULTS:

Variation of Feature described by Shape				
Feature	n	Full Shape	Cartilages	Menisci
Age	4400	10%	12%	3%
Sex	4400	67%	66%	57%
BMI	4322	23%	21%	22%
JSW	3060	24%	20%	4%
KL	4398	28%	25%	17%
WOMAC Pain	4692	7%	7%	4%



DISCUSSION: The simple linear statistical analysis does not allow the multi-modal distributions that seem appropriate given the heterogeneity of OA. Ideally, a distribution with a mode for each key OA phenotype seems appealing. Further, the simple linear analysis only partly allows capturing information that is intrinsically available from the shape model (such as JSW). Non-linear statistical analysis or more sophisticated machine learning could potentially improve on this. In particular if we extend the analysis to several OAI visits, the number of samples exceed the dimensionality of the shape models. Including several OAI visits would also allow statistical modeling beyond simple correlations, taking an important step in the direction of causality.
Even so, the simple statistics revealed that some OA-related features are captured in the joint shape model, and primarily in the subset of the model containing the cartilages. The menisci shapes mainly contain most of the variation related to BMI. A biomechanical link between BMI and meniscus shape seems very plausible.

CONCLUSION: This explorative study demonstrated that the shape of the joint correlated with several OA-related features. This may be further explored to investigate OA pathogenesis.

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DISCLOSURE: Erik Dam is a shareholder of Biomediq. The IPR for KIQ is with Biomediq.
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CAN WE EXPLAIN OSTEOARTHRITIS PAIN FROM STRCTURE AND BEHAVIOR? WITH DATA FROM THE OAI

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PURPOSE: OA pain is known to be an elusive symptom to quantify and explain. Bone marrow lesions, synovial inflammation, and stress are among the known, diverse correlates. In this study, we investigate if a big data approach using the baseline OAI scans and non-pain-related questionnaires will add to the understanding of OA pain.

METHODS: We analyzed the baseline MRIs from the right knees in Osteoarthritis Initiative (OAI). Segmentation and shape was performed using the Knee Imaging Quantification framework (KIQ) resulting in a multi-tissue shape model for each of the 4695 analyzed MRIs. For cartilages and menisci we quantified volume, area, thickness, cavity, smoothness and homogeneity. This MRI data was combined with the radiological Kellgren-Lawrence grade (KL) and joint space width (JSW), demographic variables (age, BMI, sex), semi-quantitative radiological readings (MOAKS, BLOKS) and all non-outcome-related variables for the OAI AllClinical00 collection. We excluded variables with scores for less than 4300 subjects and used simple median imputation for missing values. We performed sequential floating feature selection to add variables into a k-Nearest Neighbor model. We used this model to estimate pain by performed extrapolation from the k neighbors. The relationship to pain was quantified by the root-mean-squared error (RMSE) and the Pearson linear correlation coefficient (r) compared to the WOMAC right knee pain score.

RESULTS:

Variable groups included	Variables selected	RMSE	r^2
JSW/KL	KL	3.15	5.6%
KIQ	ThCtAB.MT, Hom.MT, iStd.MT, VC.LT, CavR.MF, Hom.MF, Smooth.MF, ThCtAB.LF, Area.P, iStd.MM, iStd.LM	3.10	9.5%
KIQ + JSW/KL	ThCtAB.MTC, Hom.MT, VC.LT, CavR.MF, Hom.MF, Smooth.MF, ThCtAB.LF, Hom.LF, Area.P, Smooth.P, KL	3.08	10.0%
KIQ + JSW/KL + Demographics	KL, BMI, Smooth.MT, CV.LT, ThCtAB.MFA, Hom.MF, iStd.MF, Smooth.MF, ThCtAB.LFA, Smooth.P, Age	3.03	12.6%
KIQ + JSW/KL + Demographics + Clinical	V00SF3, V00SF4, V00SF5, P01RSXKOA, V00RKPATPN, V00RKRFXPN, V00RKMTTPN, P01RXRKOA, V00EDCV	2.52	42.0%

DISCUSSION: We demonstrated the feasibility of a Machine Learning approach for suggesting structural sources of pain in OA. Further, clustering approaches based on the kNN model metric that may provide the foundation for future phenotype investigations. The semi-quantitative radiological readings were excluded since they were only available for up to 1200 right knees. This excluded very relevant OA features such as BML. Even so, we demonstrated that structural imaging markers contributed to understanding pain in OA (with r^2 at 10%). A main challenge in using the more than 1000 variables in OAI was the elimination of outcome-related variables (e.g. KOOS pain is correlated with WOMAC pain). The current resulting model included VOOSF variables quantify “physical health” limitations that may directly include pain. And the P01RXRKOA and P01RSXKOA are calculated variables derived from several indicators of radiographic and symptomatic OA. These variables should likely be eliminated from the analysis.

CONCLUSION: The large epidemiological cohorts are well suited for big data analysis. However, even using all the OAI baseline data, understanding pain continues to be a work in progress.

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DISCLOSURE: Erik Dam is a shareholder of Biomediq. The IPR for KIQ is with Biomediq.
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DO AHLBÄCK-SCORES IDENTIFY SUBGROUPS WITH DIFFERENT RATES OF CARTILAGE THICKNESS LOSS IN PATIENTS WITH MODERATE TO SEVERE RADIOGRAPHIC OSTEOARTHRITIS? DATA FORM THE OSTEOARTHRITIS INITIATIVE

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INTRODUCTION: The Kellgren Lawrence grade (KLG) is commonly used for patient selection and stratification in clinical trials such as the Osteoarthritis Initiative (OAI). Moderate and severe radiographic knee OA is usually defined as KLG 3 and 4, with KLG 4 equivalent to end-stage knee OA. Yet, the Ahlbäck knee OA radiographic grading system (1-5) has been developed for identifying different subtypes of advanced knee OA (i.e. KLG 3 or 4), whereas KLG 3 and 4 knees have been shown to display similar rates of cartilage loss (and sensitivity to change) by MRI [1].

OBJECTIVE: To investigate whether Ahlbäck scores are able to differentiate rates of cartilage loss (and sensitivity to change) in KLG-3 and -4 knees.

METHODS**:** From baseline fixed flexion radiographs, Ahlbäck scores were read by SH in N=108 OAI participants with KLG 4 according to site readings. One-year femorotibial cartilage thickness change was determined in these participants from coronal FLASH water excitation MRIs acquired at baseline and at year 1 follow-up. The cartilage thickness change was determine for the entire femorotibial joint (FTJ) , the medial compartment (MFTC), the lateral compartment (LFTC) and 16 femorotibial subregions, using Chondrometrics software (Chondrometrics Gmbh, Ainring, Germany). Location-independent ordered values 1 and 16 (OV1/OV16) representing the sub regions with largest loss (OV1) and gain (OV16) were also calculated for each knee. One-year change in cartilage thickness was compared between Ahlbäck scores using ANOVA.

RESULTS: Of the 108 knees with KLG 4 in site readings, n=30 / 33 / 36 / 9 / 0 were grades as Ahlbäck 1 / 2 / 3 / 4 / 5. According to OAI central readings (Boston University), n=30 / 78 knees were graded as KLG 3 / 4. Comparing the cartilage thickness variables between Ahlbäck groups in an ANOVA showed no statistical significant difference for FTJ, MFTC, LFTC and OV1, but for OV16 the p-value at 0.03 indicates differences between groups (Table).

Table: One-year change in knees stratified by Ahlbäck

[µm]	Ahlbäck 1		Ahlbäck 2		Ahlbäck 3		Ahlbäck 4		P-Value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	(ANOVA)
MFTC	-0.05	0.13	-0.09	0.18	-0.04	0.11	0.01	0.17	0.20
LFTC	-0.04	0.10	-0.05	0.12	-0.04	0.10	-0.05	0.21	0.99
OV 1	-0.18	0.09	-0.21	0.12	-0.19	0.11	-0.22	o.14	0.63
OV 16	0.11	0.07	-0.11	0.06	0.12	0.06	0.19	0.17	0.03

CONCLUSION: Radiographic grading of knees with moderate to severe OA using the Ahlbäck-scores did not identify subtypes within KLG 3 and 4 knees that displayed greater or lesser rates (and sensitivity to) change than other subtypes.

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MECHANICAL STRESS AT THE PROXIMAL TIBIA IS RELATED TO KNEE PAIN IN PATIENTS WITH KNEE OSTEOARTHRITIS: A SUBJECT-SPECIFIC FINITE ELEMENT STUDY

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INTRODUCTION: OA-related pain may be related to many contributing factors (e.g., alignment, BMLs, attrition, subchondral cysts, altered bone mineral density (BMD), psychosocial factors), thus it is important to incorporate a whole-joint approach when assessing the role of bone in OA-related pain pathogenesis. Subject-specific finite element (FE) modeling is a non-invasive technique able to incorporate regional variations in bone structure, material properties, and geometry as well as accounting for limb alignment. Our group previously applied subject-specific FE modeling to identify differences in mechanical quantities (stress, strain, stiffness) between knees with and without OA. However, it is unclear if these mechanical quantities are associated with OA-related pain.

OBJECTIVE: The objectives of this study were to: 1) assess relationships between FE-derived mechanical quantities (stress, strain, stiffness) and clinical characteristics of OA (OA severity, OA-related pain, alignment) in patients with knee OA, and 2) compare mechanical quantities across patients with differing levels of OA-related knee pain to those reporting no knee pain.

METHODS: The preoperative knee of 42 total knee replacement patients was scanned using quantitative CT. Pain was measured using the WOMAC and participants were categorized into three groups based on their pain score while lying in bed at night: 'no nocturnal pain' (score of 0 to 1), 'moderate nocturnal pain' (score of 2), and 'severe nocturnal pain' (score of 3 or 4) as based on our previous study evaluating subchondral BMD. We used subject-specific FE modelling to acquire medial and lateral proximal tibial stiffness, as well as principal compressive stress and strain of cortical and trabecular bone of subchondral, epiphyseal, and metaphyseal regions of the proximal tibia. All knees were aligned in a neutral position and an equivalent load of one body-weight was applied. We assessed relationships between clinical characteristics of OA and mechanical outcomes using Spearman's rank correlation (ρ). We contrasted regional mechanical quantities (stress, strain, stiffness) of moderate and severe nocturnal pain groups to those from no nocturnal pain group using MANCOVA with age and sex as covariates.

RESULTS: Principal compressive stress at most lateral regions was positively associated with nocturnal pain, with ρ ranging from 0.33 to 0.50 (p<0.05). Principal compressive stress at the lateral region was 47 to 65% higher in participants with severe pain than in participants with no pain (adjusted mean differences ranged from 0.06 to 0.13 MPa). There were no differences in medial or lateral principal compressive strain or stiffness between pain and no pain groups.

CONCLUSION: Our findings indicate that pain is related to the compressive stress placed upon osteoarthritic bone. Pain may be associated with bone remodeling, potentially initiated by mechanical stress approaching (or exceeding) bone tissue's yield strength. These early results identify mechanical outcomes to target when investigating the role of bone in OA-related pain, and emphasize the importance of evaluating the mechanical role of bone in OA-related pain pathogenesis.

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DISCLOSURE STATEMENT: None
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IS MRI DEFINED OA ASSOCIATED TO THE COURSE OF KNEE SYMPTOMS IN ASYMPTOMATIC OVERWEIGHT AND OBESE WOMEN OVER 6.5 YEARS?

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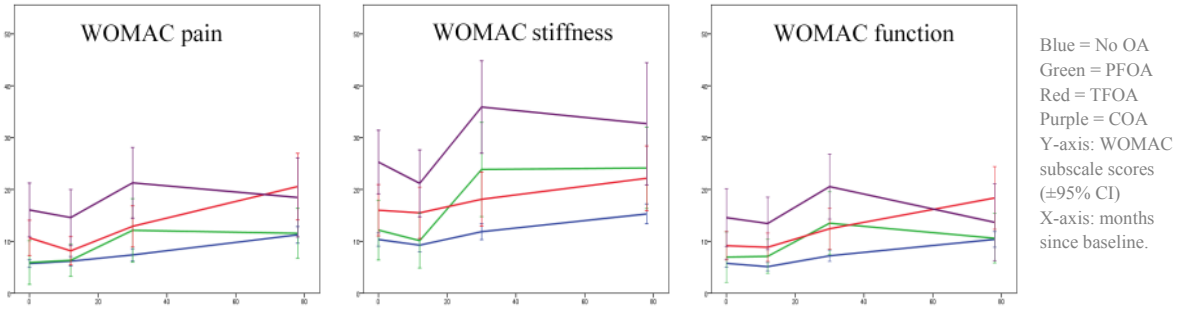
INTRODUCTION: Whether MR imaging can help identify subjects at risk for developing knee complaints is still uncertain. One of the factors that might be associated with the course of knee complaints is the involvement of the patellofemoral compartment.

OBJECTIVE: To assess whether MRI-defined patellofemoral osteoarthritis (PFOA) or tibiofemoral osteoarthritis (TFOA) was associated with the course of knee complaints over 6.5 years follow-up in overweight and obese middle-aged women free of knee OA at baseline.

METHODS: Data from the PROOF study (PRevention of knee Osteoarthritis in Overweight Females) were used. Women in the Rotterdam region between 50 and 60 years with a BMI $\geq$ 27 kg/m^2, but free of clinical knee osteoarthritis were included. At baseline and after 6, 12, 18, 24, 30 months and 6.5 years, the WOMAC questionnaire was obtained from all participants. At baseline, a multi-sequential 1.5 Tesla MRI was obtained for both knees of all subjects. All knees MRI's were scored using the MOAKS. Based on the MOAKS features, MRI OA (using the published criteria by Hunter et al. 2011) was defined for the patellofemoral and tibiofemoral compartments. Using Generalized Estimated Equations, with both knees and the follow-up time-points as repeated measures, the course of the WOMAC pain, function, and stiffness subscales (0-100) was determined for knees with isolated PFOA, isolated TFOA and combined PFOA and TFOA (COA), compared to knees free of MRI defined OA (adjusted for age, BMI, varus alignment, injury, menopausal status, Heberden's nodes).
RESULTS: Mean baseline age was 55.7 years (SD ±3.2) years and mean BMI 32.4 kg/m^2 (SD ±4.3). At baseline, no significant differences in pain, function and stiffness were found between knees without OA and knees with PFOA. Knees with TFOA had significantly higher scores on the subscales of pain and stiffness, while knees with COA had significantly higher scores at baseline on all WOMAC subscales, compared to knees without OA at baseline. No significant difference were found on the longitudinal change between groups.



CONCLUSION: Although knees with TFOA and COA had slightly increased WOMAC scores at baseline compared to knees with PFOA or no OA, the longitudinal course was identical for knees without MRI defined OA, isolated PFOA, isolated TFOA, and COA. Therefore, knees with PFOA, TFOA or COA were not at increased risk for statistically significant or clinical relevant increases in knee symptoms over a 6.5 year period.

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KNEE STRUCTURAL LESIONS IN JOINTS WITHOUT OSTEOARTHRITIS AND IMPACT ON LONGITUDINAL CHANGE IN TIBIO-FEMORAL CARTILAGE T2 VALUES

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INTRODUCTION: Structural MRI-defined pathology of the knee joint has been observed in subjects without radiographic abnormalities or knee pain. Cartilage transverse relaxation time (T2) has been suggested as a compositional endpoint for measuring progression of knee OA at its earliest stages. However, it is currently unknown whether structural pathology drives T2 changes in knees without radiographic signs of OA or pain.

OBJECTIVE: To investigate whether MRI features such as effusion-synovitis, Hoffa-synovitis, bone marrow lesions (BMLs), prevalent cartilage lesions, meniscus damage and meniscus extrusion are associated with subsequent change in laminar (superficial and deep layer) cartilage T2 in the femorotibial joint of participants from the OAI healthy reference cohort over 1 and 4 year observation periods.

METHODS: The study included all 82 participants from the OAI healthy reference cohort without radiographic OA as defined by the central X-ray readings (Kellgren-Lawrence grades 0 in both knees) and with longitudinal image acquisitions. Structural MRI pathology in the right knee was assessed by an experienced radiologist (F.R.) using the semi-quantitative MOAKS scoring system. Cartilage T2 relaxometry was performed in the same knees using sagittal multi-echo spin-echo MRIs. Deep and superficial layer (each 50% of cartilage thickness) cartilage T2 times were computed after manual segmentation of the medial and lateral femorotibial compartment (MFTC/LFTC). Baseline and year-one follow-up T2 times were available for all 82 participants. Year-four follow-up was available for 57 of the 82 participants. Due to low frequencies of knee joint structural lesions at baseline and the relatively small sample size, the MOAKS subscales were dichotomized into presence or absence of the respective features. Compartment-specific analysis of factors associated with superficial or deep layer T2 change in the MFTC or LFTC over 1 or 4 years was performed using UNIANOVA, including knee-specific features (Hoffa-synovitis and effusion-synovitis) and compartment-specific features (bone marrow lesions, cartilage lesions, meniscus morphology, and meniscus extrusion).

RESULTS: The sample included 50 women and 32 men (mean age 54.1±7.2y, BMI 24.2±3.0 kg/m²). Of these, 15 (18%) had any baseline morphologic cartilage damage in the MFTC and 26 (32%) in the LFTC (superficial damage only), 39 (48%) knees had any baseline Hoffa-synovitis, 13 (16%) any effusion-synovitis, 7 (9%) knees had medial and 3 (4%) had lateral femorotibial BMLs, 7 (9%) had medial and 3 (4%) lateral meniscal damage (excluding intra-meniscal signal alterations) or meniscus extrusion (extrusion > 3mm only). Most structural articular lesions at baseline did not predict change in ipsi-compartmental longitudinal T2 at Y1 or Y4. Statistically significant associations were observed between presence of baseline MFTC osteophytes and a prolongation in the superficial layer T2 over 1- year (0.8 vs. 0.0 ms, p=0.02), and 4-year observation periods (2.3 vs. 0.9 ms, p=0.01). Further, the presence of baseline MFTC meniscal damage or extrusion appeared to be associated with a prolongation in deep T2 times at Y1 (2.1 vs. 0.7 ms, p=0.02). Laterally, concurrent worsening of MRI features was associated with ipsi-compartmental T2 shortening in superficial and deep layers, but no such relationship was seen in the medial compartment. Further, ipsi-compartmental worsening of MRI features from baseline to Y1 was not associated with subsequent change in T2 from Y1 to Y4 in the MFTC or LFTC. The total number of baseline MRI pathologies was not significantly associated with a change in T2 times in the MFTC or LFTC over 1 or 4 years.

CONCLUSION: In this cohort, most structural MRI lesions at baseline did not predict change in ipsi-compartmental longitudinal T2. Statistically significant associations were only observed for presence of medial osteophytes and medial meniscal damage with subsequent T2 change in the superficial and/or deep layer; however, these relationships did not account for multiple statistical testing. The study therefore does not provide evidence that cartilage T2 is a sensitive tool for monitoring the effect of structural MRI pathology on compositional progression during the potentially earliest phases of the disease.

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THREE-DIMENTIONAL MRI FOR DEPICTION OF CRUCIATE LIGAMENT INJURIES: A META-ANALYSIS OF DIAGNOSTIC PERFORMANCE

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INTRODUCTION: Three-dimensional (3D) magnetic resonance imaging (MRI) sequences could potentially improve efficiency and quality of musculoskeletal imaging, since they provide a single isotropic data set which allows multi-planar reformation. However, there is still an ongoing debate on the fact that whether this technique could replace conventional two-dimensional (2D) MRI in clinical practice for detecting cruciate ligament injuries.

OBJECTIVE: To evaluate diagnostic performance of 3D MRI in the depiction of cruciate ligament injuries, using surgery or arthroscopy as the standard of reference.

MATERIALS AND METHODS: A comprehensive literature review was performed employing several databases. Original articles evaluating diagnostic performance of 3D MRI were included. Pooled values of sensitivity, specificity and diagnostic odds ratio (DOR) were calculated. To assess the effect of relevant co-variates on diagnostic performance of 3D MRI, sensitivity analysis was performed.

RESULTS: Out of 731 identified records, 21 studies (1278 3D MRI examinations) were included. Specificity and sensitivity of 3D MRI studies were 96.2% (95% confidence interval (CI): 93.9%-97.7%) and 91.5% (95%CI: 87.6%-94.3%), respectively. Fourteen studies reported the results of simultaneous 2D MRI examinations and the pooled sensitivity and specificity of these 2D MRI examinations were 91% (95%CI: 86%-95%) and 97% (95%CI: 94%-98%), respectively. The likelihood scattergram revealed the capability of 3D MRI in confirming and excluding anterior cruciate ligament (ACL) injuries. Regarding posterior cruciate ligament (PCL), 3D MRI was only able to confirm the injury. 3D MRI performed with 3T magnetic field had significantly higher DOR compared with 3D MRI performed with 1.5T or lower scanners (relative DOR: 6.67, P-value=0.008). FSE sequences had higher sensitivity than GRE sequences in detecting cruciate ligament injuries (P-value=0.003). Multi-planar reformation (MPR) also improved the sensitivity of 3D MRI in detecting cruciate ligament injuries (P-value=0.002).

CONCLUSION: 3D MRI appeared equivalent to 2D MRI examinations in the diagnosis of cruciate ligament injuries. FSE sequences and using MPR technique improve sensitivity of 3D sequences in detecting cruciate ligament injuries. 3D MRI is capable of confirming presence of an injury in abnormal cruciate ligaments. This modality can also exclude presence of injury in a normal ACL.

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THE ASSOCIATION BETWEEN UNDIFFERENTIATED ARTHRITIS / PRE-RHEUMATOID ARTHRITIS AND LONGITUDINAL MRI-BASED KNEE OSTEOARTHRITIS WORSENING: THE FNIH STUDY

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INTRODUCTION: Shared inflammatory pathophysiology of osteoarthritis (OA) and inflammatory joint diseases such as Rheumatoid Arthritis (RA) have been suggested previously. Undifferentiated arthritis (UA) and Pre-RA are considered as early stage inflammatory arthropathy before the diagnosis of RA based on clinical criteria; However, UA may persist without ultimate progression to RA.

OBJECTIVE: We aimed to investigate the association between knee OA structural damage worsening and clinically defined UA/Pre-RA using 3T-MRI measurements.

METHODS: This was an IRB-approved and HIPAA-compliant study of 600 subjects from the FNIH project. At the baseline visit, subjects with physician-diagnosed RA were excluded. Participants with any signs of arthritis, but not diagnosed RA, were assessed by connective tissue disease RA screening questionnaire and knee radiography. After exclusions of possible RA subjects (using questionnaire/radiography), the remaining were regarded as UA. Any of the UA-(control) or UA+ subjects who have developed RA in follow-up visits were categorized as Pre-RA. Baseline and 24-month semi-quantitative MRI OA Knee Score (MOAKS) measures of study groups were extracted and analyzed. Logistic regression model, adjusted for age, sex, BMI, and smoking status was used to assess the association between UA/pre-RA and baseline/worsening of MRI-based OA-related structural damages including cartilage thickness/surface scores, Hoffa-synovitis, and effusion-synovitis.

RESULTS: Presence of UA was associated with nearly significant structural damage in cartilage surface/thickness scores of whole knee (OR (95%CI): 1.73(0.94-3.1) and 1.73(1.0-3.04)), especially in patellofemoral joint (OR: 2.05(1.16-3.62) and 1.76(0.99-3.07)). In longitudinal assessment, presence of UA was significantly associated with 24-month worsening of lateral tibiofemoral cartilage damage (OR: 2.46(1.1-5.07). Pre-RA was not significantly related to cartilage damage after adjustments. There was also no association between UA/pre-RA and knee Hoffa-synovitis/effusion-synovitis.

CONCLUSION: Positive history of UA is associated with the concurrent knee joint cartilage defects at baseline, and its worsening over 24-months. Knee OA characteristic cartilage defects are probable in UA subjects despite absence of knee effusion/synovitis. This finding warrant further investigations for altered OA outcomes in subjects with UA but not definitive RA diagnosis.

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ASSOCIATION OF TROCHLEAR DYSPLASIA WITH MRI-BASED PATELLOFEMORAL OSTEOARTHRITIS WORSENING: THE FNIH STUDY

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INTRODUCTION: Trochlear dysplasia has been shown to be associated with patellofemoral (PF) osteoarthritis (OA) in previous cross-sectional studies.

OBJECTIVE: In this study, we investigated the association between trochlear groove depth (TGD), a commonly used metric for determination and quantification of trochlear dysplasia using MRI, and PF OA-related structural damage worsening using baseline and 24-months follow-up MRI examinations.

METHODS: The FNIH OA Biomarkers Consortium project is a nested case-control study within the OAI study, which is the largest ongoing study of knee OA, enrolling 600 subjects. All FNIH participants were included in our study. Data on clinical findings and semi-quantitative MRI OA Knee Scoring (MOAKS) of PF OA-related features were extracted, in addition to axial MRI sequences that were used to measure the TGD in each knee by two musculoskeletal radiologists in a blinded fashion (as the average lateral and medial anteroposterior diameters of trochlear facets minus diameter of deepest point of sulcus (Figure:[(a+c)/2)]-b)). Association of TGD measurements with baseline PF joint (patella and trochlear sub-regions) cartilage, bone marrow lesion (BMLs), and osteophytes MOAKS scores and their worsening after 2-years of follow-up were studied using regression models (adjusted for possible confounders, Figure) and reporting odds ratio (OR) in each model.

RESULTS: Higher TGD measures are associated with surface cartilage defects in medial (OR (95% confidence intervals)=1.16(1.05-1.28)) and lateral (OR=1.13(1.02-1.26)) trochlea, in addition to higher size (1.18(1.05-1.33)) and number (1.18(1.05-1.33)) of BMLs in medial trochlea. However, results on the analysis of worsening of MOAKS scores after 2-years were not significant in medial or lateral regions of patella and trochlea.

CONCLUSION: Higher TGD measure is associated with baseline medial and lateral trochlear cartilage defects and medial trochlear BMLs in PF compartment, but no corresponding worsening was identified using 24-months follow-up MRI examinations. TGD measures, as a measure of trochlear dysplasia, is associated with the cross-section OA-related features in trochlear but not patellar sub-regions. Follow-up MRI examinations longer than 24 months may be warranted to detect potential longitudinal worsening of these structural damages.

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ASSOCIATION OF PATELLA ALTA WITH MRI-BASED PATELLOFEMORAL OSTEOARTHRITIS: DATA FROM THE OSTEOARTHRITIS INIATIVE

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INTRODUCTION: Patella alta leads to diminished stability of the patellofemoral joint during knee motion, especially during knee extension. Several recent studies suggested patella alta as a possible risk factor for patellofemoral osteoarthritis (OA). The large database of subjects with or at-risk of knee OA in the Osteoarthritis Initiative (OAI) cohort, provide the opportunity to assess the contributing role of patella alta (measured by Insall-Salvati ratio (ISR)) in developing patellofemoral OA.

OBJECTIVE: To determine the association between ISR, a measure of patella alta, and MRI-based OA-related patellofemoral joint structural changes at baseline and worsening over 24-month in participants of the OAI.

METHODS: The study was IRB-approved and HIPAA-compliant. The ISR was measured in 600 subjects using baseline sagittal 3T-MRI plane by two radiologists. Baseline and 24-month MRI Osteoarthritis Knee Score (MOAKS) variables for patellofemoral bone marrow lesions (BMLs), cartilage defects, and osteophytes were available and extracted from the OAI database, and the concurrent associations between ISR and these 3T-MRI features and worsening over 24 months were evaluated using regression analyses. After computing receiver operating characteristic curves, the optimal cutoff point of ISR for indicating patellofemoral OA at baseline and its worsening were determined.

RESULTS: In baseline analysis, higher ISR was associated with increased odds of patellofemoral BMLs (odds ratio(OR)(95% confidence interval): 3.41(1.45–8.06), and number of BMLs in the patella: 3.47(1.44 – 8.37)), as well as patellar cartilage damage (OR for surface score:3.16(1.26–7.9), for full-thickness score: 4.77(1.89–12.04)), and patellar (OR:5.44(2.18–13.57)) and trochlear (OR: 3.55(1.46–8.63)) osteophytes. In the longitudinal analysis, 24-month worsening of patellar BMLs (OR: 3.85(1.35–10.98)) was associated with higher baseline ISR. We determined the optimal cutoff point of ISR ≥1.2 for predicting concurrent patellofemoral OA structural damage (sensitivity: 46.7%, specificity: 71.7%) and for determining patellofemoral OA-related structural damage worsening after 24 months (sensitivity: 44.1%, specificity: 69.4%).

CONCLUSION: The ISR could be considered as an indicator of concurrent patellofemoral OA-related structural damages and predictor of their worsening with the optimal cutoff point of ≥1.2 using knee sagittal MRI measurements. MRI-defined patella alta (ISR ≥1.2) could be considered as the predictor of patellofemoral OA-related structural damage worsening.

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LATERAL PATELLA TILT AND MRI-BASED PATELLOFEMORAL OSTEOARTHRITIS: AN ANALYSIS FROM THE OSTEOARTHRITIS INITIATIVE

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INTRODUCTION: The patellofemoral (PF) compartment is reported with the highest frequency of osteoarthritis (OA) among the knee compartments. The possible association between the PF morphologic features such as patellar tilt and PF OA has come into attention.

OBJECTIVE: In this study, we assessed the cross-sectional/longitudinal association of lateral patella tilt (LPT) measures with OA-related features in PF compartment.

METHODS: Recorded clinical and imaging data of all 600 participants in the FNIH project, a nested case-control study within the OAI cohort which is the largest ongoing cohort studying knee OA, were extracted and analyzed. The knee MRI sequences of all subjects were read by two musculoskeletal radiologists to measure LPT (as the angle formed between lines showing the longest patella diameter and posterior aspect of both condyles). Association of LPT measures with MRI OA Knee Scoring (MOAKS) for knee OA-related features, including cartilage damage, bone marrow lesions (BMLs), and osteophytes in addition to knee cartilage volumes at baseline, and worsening of MOAKS readings and cartilage volumes after 2-year follow-up were assessed in logistic regression models adjusted for several possible confounders (Figure), and reporting odds ratio (OR).

RESULTS: In the cross-sectional part, higher LPT was associated with lower cartilage volumes in lateral tibia, femur, and patella, in addition to higher scores of surface/thickness cartilage damage (OR=1.05(1.02-1.08) and OR=1.08(1.04-1.11)), number (OR=1.06(1.03-1.09)) and size (OR=1.06(1.03-1.09)) of BMLs, and osteophytes (OR=1.07(1.04-1.11)) in lateral PF region. However, medial PF region showed lower cartilage defects and BMLs scores and higher osteophytes scores in subjects with higher LPT. In the longitudinal study, higher LPT measures were also associated with worsening of cartilage volume in lateral tibia and BMLs scores in lateral PF region.

CONCLUSION: Higher measures of LPT is associated with the progression of OA-related features in lateral patella and trochlea (2-11% increase in odds of OA progression for each degree increase in LPT), whereas it was linked with lower odds of cartilage defects and BMLs in medial trochlea. Subjects with higher LPT (patellar tilt) are at increased risk of lateral PFOA incidence and progression.

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ASSOCIATION BETWEEN PATELLOFEMORAL JOINT CARTILAGE DAMAGE WORSENING AND KNEELING ACTIVITY IN SUBJECTS WITH/WITHOUT PATELLA ALTA: THE FNIH STUDY

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INTRODUCTION: It has been suggested that kneeling in occupational/sport activities is associated with knee OA. Studies suggested the association between kneeling and tibiofemoral joint cartilage damage, but reports of patellofemoral joint (PFJ) involvement are controversial.

OBJECTIVE: We aimed to investigate whether kneeling activity is associated with the worsening of MRI measures of PFJ cartilage damage in subjects with/without patella alta (PA) using the Foundation for the National Institute of Health (FNIH) study participants.

METHODS: The study was IRB-approved and HIPAA-compliant. Baseline and 24-month follow-up semi-quantitative MRI Osteoarthritis Knee Score (MOAKS) measures of PFJ of 600 subjects from the FNIH study were extracted. At the baseline visit, subjects were asked how many days per week they participated in activities with kneeling activity ≥30 minutes. Insall-Salvati ratio (ISR) (patellar tendon/patellar height) was measured by a musculoskeletal radiologist using the baseline MRIs; knees with ISR≥1.3 were considered as PA. Logistic regression adjusted for age, sex and BMI, Chi-square test and Breslow-Day Homogeneity test were used to assess the impact of kneeling on worsening of MOAKS cartilage scores over 24-months in subjects with/without PA.

RESULTS: Worsening in MOAKS cartilage scores was seen in subjects with ≥6 days/week of kneeling activity compared to subjects with less kneeling activity (adjusted OR(95%CI): 2.95(1.08-8.07)). However, despite the trend, 2-5 days/week kneeling was not associated with worsening of PFJ cartilage damages compared to less kneeling activity (<2 days/week). Stratifying analysis showed that only PA+ subjects, not PA-, had significant association between the kneeling and worsening of PFJ cartilage damage, especially in surface cartilage score (OR: 45.01(1.40-1444.2)) and medial side (OR:44.0(4.55-425.7)). Homogeneity test demonstrated significant difference between PA+ and PA- groups (P-value: 0.005).

CONCLUSION: Kneeling activity in ≥6 days/week is associated with the worsening of PFJ MRI cartilage scores compared to less kneeling activity, especially in subjects with underlying PA. Frequent daily kneeling activity is associated with the higher risk of PFJ cartilage damage resulting in PF OA, especially in subjects with associated patella alta.

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BISPHOSPHONATE THERAPY AND MRI-BASED KNEE OSTEOARTHRITIS STRUCTURAL DAMAGE: EXPLORATORY ANALYSIS FROM THE FNIH STUDY

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INTRODUCTION: To date, existing pharmacologic agents demonstrated controversial or little disease-modifying efficacy on knee osteoarthritis (OA) progression. There is a need to identify a drug with consistent protective effects against knee OA progression.

OBJECTIVE: In this study, we aimed to determine whether bisphosphonate intake was associated with tibiofemoral OA progression.

METHODS: We analyzed data from female subjects (one index knee) from the FNIH study, which is an IRB-approved and HIPAA-compliant study. Subjects were classified as bisphosphonate users (n=56) and non-users (n=295). The association between bisphosphonate intake and radiographic joint space loss (JSL) progression (>0.7mm; using 24–48months radiographs) and osseous damage worsening (baseline–24months MRI OA Knee Score (MOAKS) changes for bone marrow lesion (BML) and osteophyte) was evaluated using logistic regression. Re-analysis was performed using conditional logistic regression model in the propensity score-matched subjects for OA and osteoporosis-related factors to address the confounding by indication bias for bisphosphonate intake. The equivalent MRI-derived subchondral trabecular bone structure metrics were also confirmed between the two matched groups.

RESULTS: Using initial adjusted regression analysis, JSL progression (odds ratio 95% confidence interval (OR (95%CI)): 0.364(0.18–0.72), P-value: 0.004) and BML worsening (OR (95%CI): 0.342(0.12–0.95), P-value: 0.039) were lower in bisphosphonate users compared to non-users. However using propensity score matching method, the above results were not significant for JSL progression (OR (95%CI): 0.594(0.32–1.10), P-value: 0.098), and were approached statistically significant BML worsening (OR (95%CI): 0.380(0.14–1.01), P-value: 0.052).

CONCLUSION: We showed that bisphosphonate intake might be associated with (approaching but not achieving significance) less subchondral bone BML worsening. Bisphosphonate intake had some protective effects on subchondral bone BML worsening. The role of BML as a possible indication for bisphosphonate use in knee OA subjects, and as the moderating variable for the protective effect of bisphosphonate is subject to future investigations.

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DISCLOSURE STATEMENT: F. Roemer is Shareholder of BICL, LLC. A. Guermazi is Shareholder of BICL, LLC and Consultant to Pfizer, TissueGene, OrthoTrophix, AstraZeneca, Sanofi, GE Healthcare and MerckSerono
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T2-MAPPING OF DEEP AND SUPERFICIAL FEMORAL CARTILAGE 3-MONTHS FOLLOWING ACL RECONSTRUCTION SURGERY

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PURPOSE: Patients who have experienced ACL tears have a significantly elevated risk of developing OA[1]. Quantitative MRI measures, such as T2, which is considered reflective of collagen content and organization have been used to track changes in cartilage following ACL injury. At 1-year post-ACL-reconstruction, elevations in T2 times have been observed[2], however it would be desirable to observe the earliest changes that lead to OA. The objective of this study was to determine if changes in T2 can be detected 3-months post-ACL-reconstruction surgery in the deep and superficial layers of cartilage.

METHODS: We scanned the ACL-reconstructed and contralateral knees of 9 subjects (5 females, ages 26-54) at a 3T MR scanner (GE Healthcare, Milwaukee, WI) using a 16-channel flexible knee coil. Subjects were scanned 3 weeks and 3 months following surgery using a double-echo in steady-state sequence (DESS) with scan parameters: FOV=160mm, matrix=384x320, $TE_1/TE_2/TR$=6, 38, 22ms, sagittal slice thickness=1.5mm, flip angle=25°. T2 values were calculated from the two DESS echoes using a simple analytical model[3]. The femoral cartilage was manually segmented from the sum-of-squares of the two DESS echoes (Seg3D, University of Utah). Femoral cartilage projections were constructed from the segmented T2 maps[4] and separated into superficial and deep layers based on the midpoint of thickness for visualization and analysis (Figure 1). For analysis, the femoral cartilage was further divided into medial and lateral sides, and then split into posterior, central and anterior regions. Differences between T2 relaxations times at 3 weeks and 3 months in the various regions for the ACL-reconstructed and contralateral knees were compared using a general linear model ($\alpha<0.05$).

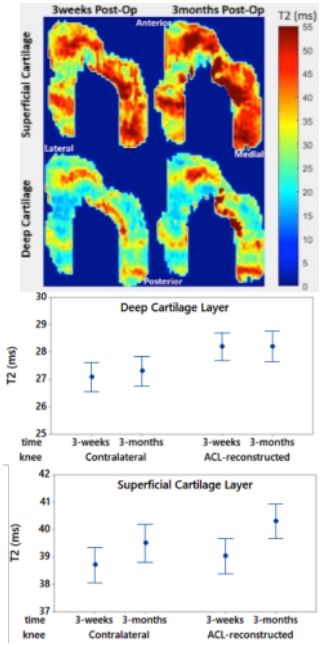

Figure 1: (Top) Femoral cartilage layers T2 map visualization. (Middle and Bottom) Mean T2 values with standard error bars for deep and superficial femoral cartilage between time points and knees.

RESULTS: We observed a trend of increasing superficial T2 relaxation times from 3-weeks to 3-months post-surgery for ACL-reconstructed (39.0± 0.6ms to 40.3±0.6ms) and contralateral knees (38.7±0.6ms to 39.5±0.7ms), which is consistent with the small increases previously seen in T2 relaxation times 1-year post-ACL-reconstruction[2]. Deep cartilage T2 appeared more consistent from 3-weeks to 3-months for both the ACL-reconstructed (28.2±0.5ms to 28.2±0.6ms) and contralateral knee (27.1±0.5ms to 27.3±0.5ms) (Fig 1). Superficial cartilage T2 relaxation times were higher in all regions compared to deep cartilage ($p<0.05$). Between knees, the lateral-central femoral cartilage T2 was significantly higher in the injured knee (mean difference of 2.3±0.6ms, $p<0.05$). Changes to T2 relaxation times between these time points could also be an effect of a subject's modified mobility and changes to weight-bearing of the injured and contralateral knees post-operatively. The creation of superficial and deep cartilage layer T2 maps allowed for improved visualization of T2 relaxation time variability (Fig 1.).

CONCLUSION: Superficial femoral cartilage T2 relaxation times increasing from 3-weeks to 3-months post-surgery for ACL injured subjects suggest that degenerative cartilage changes may be happening within 3-months of ACL reconstruction surgery. Deep and superficial cartilage T2 relaxation visualization allows for an improved qualitative method to observe T2 changes. Additional subjects are in the process of being recruited and will help further elucidate trends in cartilage T2 relaxation times following ACL-reconstruction surgery.

REFERENCES: 1 Simon AdvOrth 2015; 2 Su OA&C 2013; 3 Svensson MRI 2017; 4 Monu OA&C 2017

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DEEP LEARNING FOR BANDING ARTIFACT REDUCTION IN MUSCULOSKELETAL bSSFP

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INTRODUCTION: Balanced steady-state free precession (bSSFP) is an imaging technique that has broad applications in musculoskeletal imaging due to its desirable contrast, high signal-to-noise ratio (SNR) and fast acquisition time. However, this method is sensitive to off-resonance effects resulting in banding artifacts, which can degrade image quality. Effective band mitigation strategies typically require the acquisition of four or more phased-cycled bSSFP images, leading to long scan times.

OBJECTIVE: To develop an effective method for banding artifact reduction using deep learning to reduce the required number of phased-cycled bSSFP acquisitions, thus reducing scan time.

METHODS: A banding artifact reduction method was modeled using a deep neural network. This network was designed and trained using the U-Net architecture (a convolution network architecture typically used for image segmentation). The truth data set was generated using four phase-cycled bSSFP images combined with the elliptical signal model[1], a robust technique for eliminating banding when at least four acquisitions are acquired. The model was trained using two phase-cycled images and the generated truth data. Complex data (magnitude and phase) were used for all training and testing, as significant information on banding characteristics is contained in the image phase. Four phased cycled images were taken from phantom and in-vivo 3T MRI experiments. A small dataset of these images was generated as a proof of concept. These images had a FOV of 250mm, an acquisition matrix of 256x256x128, a slice thickness of 1mm, a TE of 2.3ms, and a TR of 4.6ms.

RESULTS: After training, the proposed algorithms were able remove banding in the images using two phased cycled images.

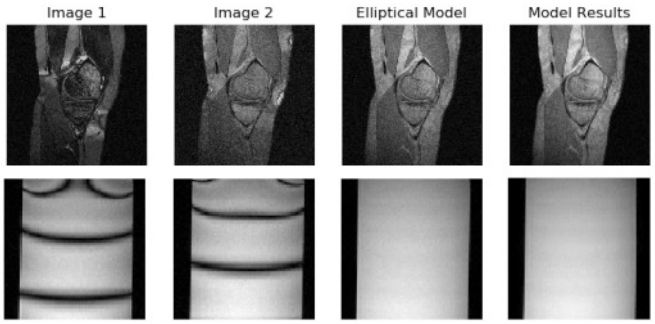

Figure 1: bSSFP images for knee (top) and phantom (bottom). From left to right: Images shown are two phased-cycled bSSFP images, an image generated from the elliptical signal model and the image generated from our deep neural network model.

CONCLUSION: Using a deep learning model with the U-Net architecture, it may be possible to reduce the number of phase-cycled bSSFP acquisitions required for robust band suppression from four to two, cutting the required scan time in half. We demonstrated a basic proof-of-concept technique on both phantom and in-vivo 3T MRI data.

REFERENCES: 1. Xiang Q, Hoff M. Magnetic Resonance in Medicine 2014

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ACKNOWLEDGEMENT: A. Chaudhari is to be thanked for his knowledge and technical assistance
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DOMAIN ADAPTATION FOR SEGMENTING CARTILAGE WITH LIMITED TRAINING DATA

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INTRODUCTION: Recent efforts in automated deep-learning-based cartilage and meniscus segmentations have relied on the OAI iMorphics dataset, which consists of manual segmentations of the cartilage and menisci for 3D DESS scans[1]. While this dataset is an excellent starting point for training convolutional neural networks (CNNs), the underlying DESS sequence was optimized over a decade ago. In addition to morphological changes that can be assessed with 3D DESS, recent advancements in qMRI have made it promising to study early-stage compositional changes through the study of biomarkers such as T_2 and T1rho. However, due to the lack of available training data, there is limited work being performed in developing robust segmentation routines for images obtained with varying pulse sequences and contrasts.

OBJECTIVE: To establish a framework for automated segmentation domain adaptation – learning a CNN segmentation initially from the OAI iMorphics dataset and then applying that knowledge to arbitrary pulse sequences with very limited training data. We demonstrate such domain adaptation segmentation using only ten knees scanned with a quantitative DESS (qDESS) sequence, which consists of two independent contrasts and T_2 relaxation times, and has shown to provide concurrent morphometry and T_2 relaxometry[2].

METHODS: We utilized a pre-trained 2D CNN, entitled Seg-CNN, which has demonstrated a dice coefficient (DC) femoral cartilage segmentation accuracy of 89.9 ± 1.6%. Seg-CNN was initially trained, validated, and tested on 60, 14, and 14 subjects respectively (two time points each) obtained from the OAI iMorphics dataset. Domain adaptation was performed by using Seg-CNN to segment femoral cartilage of subjects scanned with qDESS. 10 manually segmented subjects were used for training, and 4 each for validation and testing (all with two timepoints each). qDESS is different than the OAI DESS as it automatically generates two separate DESS echoes with varying contrasts, as well as an automatic T_2 map. OAI DESS contrasts were simulated by performing a sum-of-squares addition of the two qDESS echoes. The impact of training qDESS with the simulated OAI DESS contrasts (termed 'OAI Simulated') as well as the rich triple-contrasts (echo 1, echo 2, and T_2 map termed 'qDESS Triple') was studied. The impact of training a network from scratch versus resuming training from the OAI DESS Seg-CNN was also studied.

RESULTS & DISCUSSION: Using domain adaption by using convolutional filter weights from Seg-CNN to learn underlying femoral cartilage anatomy from the OAI DESS scans produced higher accuracy than training a network from scratch. Additionally, utilizing the rich contrasts available with the three contrasts of qDESS (echo 1, echo 2, T_2 map) produced significantly higher segmentation accuracy ($p<0.05$, Wilcoxon signed-rank test) than the OAI-Simulated contrasts, which combines the two DESS echoes into a single image. The low accuracy and lack of a significant difference ($p=0.46$) between the qDESS Triple and OAI Simulated contrast for a network trained from scratch, suggests that 10 datasets are too few to learn a CNN with 34 million free parameters.

Study	Contrasts	Training Start	Dice Accuracy
1	qDESS Triple	Seg-CNN	85.6 ± 4.1
2	OAI Simulated	Seg-CNN	82.6 ± 2.7
3	qDESS Triple	Scratch	33.9 ± 14.9
4	OAI Simulated	Scratch	42.5 ± 5.8

Table 1: Femoral cartilage segmentation accuracies for varying domain adaptation methods and image contrasts.

CONCLUSION: Domain adaptation was used to efficiently train a segmentation CNN with only 10 knees, and that the unique qDESS contrasts, can enhance segmentation accuracy, make it an ideal sequence for OA imaging.

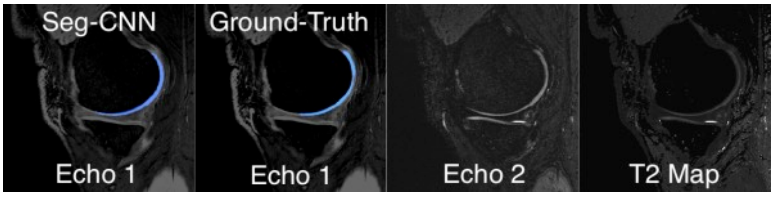

Fig. 1: Example segmentation and contrasts for qDESS

REFERENCES: 1.Norman Rad. 2017; 2.Chaudhari JMRI 2017.

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DISCLOSURE: AC has consulted for Skope MR Technologies and Subtle Medical
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USING ARTIFICIAL INTELLIGENCE TO ENHANCE MRI EFFICIENCY FOR IMAGING OA

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INTRODUCTION: High-resolution knee MRI is beneficial for measuring subtle morphological changes of thin tissues like cartilage for researching OA progression[1]. However, high resolution MRI scans such as DESS from the OAI require 11 minutes per scan, which can lead to motion artifacts and increased scan protocol durations and costs[2]. While techniques such as interpolation may be used to reduce scan time and enhance MRI resolution, they typically blur fine details in images, which is not ideal for OA studies.

OBJECTIVE: Use artificial intelligence (AI) to enhance the through-plane resolution and efficiency of MR imaging. Specifically, we generate high-resolution MR images from 3x lower resolution images. We also fully automated cartilage segmentation to demonstrate that unlike naïve interpolation, the proposed resolution enhancement method does not blur out cartilage and affect morphological quantification.

METHODS: We develop two 3D convolutional neural networks (CNNs) – one each for resolution enhancement (Res-CNN) and segmentation (Seg-CNN). Res-CNN employs a fully convolutional model while Seg-CNN employs a U-Net model[3,4]. Seg-CNN was used to validate Res-CNN since unlike manual methods, Seg-CNN is repeatable, where in the absence of blurring, segmentations would be identical between the ground-truth and Res-CNN images. Both networks were trained using 3D DESS sequences from the OAI (slice thickness = 0.7mm)[1]. 176 patients were split into 124/35/17 for training, validation, and testing, respectively. All datasets had manual femoral cartilage segmentations available. Low-resolution images with 3x thicker slices were synthesized from the high-resolution DESS data. Resolution enhancement and segmentation enhancement were also compared to tricubic interpolated (TCI) images. Image quality of the Res-CNN and TCI was compared to the ground-truth using structural similarity (SSIM) - a metric of perceptual image quality (bounds of 0-100). Image quality of the ground-truth, TCI, and Res-CNN images was assessed by two musculoskeletal radiologists (1=poor, 5=excellent). Segmentation was performed on the ground-truth, TCI, and Res-CNN images. Dice coefficients (DC) evaluated segmentation accuracy. Wilcoxon signed-rank tests evaluated Res-CNN and TCI SSIM differences (compared to the ground-truth), image quality differences, and Res-CNN and TCI segmentation DC (compared to the ground-truth).

3D Res-CNN Performance			
	Ground-Truth	Res-CNN	TCI
SSIM	N/A	79.1 ± 1.3	73.8 ± 1.3*
Quality	4.4±0.5	3.8±0.8†	3.1±1.0†*
3D Seg-CNN Accuracy			
	Ground-Truth	Res-CNN	TCI
DC	90.2 ± 1.8	89.6 ± 2.0	86.3 ± 3.2†

Table 1: Res-CNN and Seg-CNN metrics. *: ($p<0.01$) vs Res-CNN †: ($p<0.05$) vs ground-truth.

RESULTS & DISCUSSION: All quantitative results are shown in Table 1 and example images are shown in Fig. 1. Res-CNN had higher SSIM than TCI images ($p<0.05$). In the reader study, ground-truth images had the highest quality, however Res-CNN had higher quality ($p<0.05$) than TCI. For segmentation, Res-CNN had near-identical DC as the ground-truth, while TCI had significantly worse DC ($p<0.01$). The ground-truth and Res-CNN segmentations had a DC of 97±1%, demonstrating minimal image blurring.
Res-CNN outperformed the commonly-used TCI method for enhancing through-plane resolution as assessed quantitatively and by radiologists, which could be used to expedite the lengthy DESS acquisition.

CONCLUSION: We have used AI to transform low-resolution MRI into threefold higher-resolution MRI, without affecting cartilage morphometry, for reducing MRI scan time required in OA protocols.

REFERENCES: 1. Eckstein OAC 2014. 2. Peterfy OAC 2006. 3. Chaudhari MRM 2018. 4. Ronnenberger MICCAI 2015.

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DISCLOSURE: AC provides consulting services for Skope MR Technologies and Subtle Medical.
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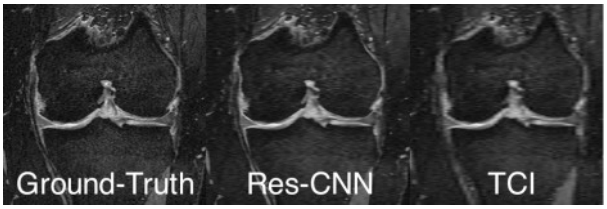

Figure 1: *Coronal ground-truth, Res-CNN, and TCI images.*

MRI FOR THE EVALUATION OF KNEE SYNOVITIS IN OSTEOARTHRITIS: COMPARISON OF CONTRAST ENHANCED AND NON CONTRAST ENHANCED: A METAANALYSIS

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INTRODUCTION: On contrast-enhanced (CE) magnetic resonance imaging (MRI), knee synovitis in osteoarthritis is usually characterized by thickened and contrast-enhancing synovial membrane. Recent studies have suggested that non-contrast-enhanced (NCE) MRI can accurately detect synovitis.

OBJECTIVE: To assess and compare the correlation of CE MRI to NCE MRI in knee osteoarthritis with histology as the reference standard.

METHODS: A comprehensive literature search was performed and related articles which were published through March 2018 were extracted. Studies were included if they reported data on MRI results with their corresponding histology. Spearman correlation of MRI results with histology reports were pooled and Cochrane Q index and I2 were calculated. Fix or random effect models were recruited to summarize the results based on the level of observed heterogeneity. To evaluate presence of publication bias, egger regression test was performed.

RESULTS: Our literature search identified 676 related articles on synovitis associated with osteoarthritis. Of these, 25 eligible articles were evaluated at the level of full text. Eight studies consisting of 268 CE MRI exams were included. Only two studies reported the correlation of NCE MRI with histology (69 knees). CE MRI were significantly correlated with macroscopic ($r=0.48$, $P<0.001$) and microscopic ($r=0.61$, $P<0.001$) histology. NCE MRI were significantly correlated ($r=0.44$ (0.23-0.62), $P<0.001$) with microscopic histology. When correlation coefficients of CE and NCE MRI with histology were compared, the difference approached but did not reach statistical significance ($P=0.051$). CE MRI were significantly correlated with inflammatory infiltrate ($r=0.43$) and cell number of ($r=274$) synovial lining as well as level of fibrosis ($r=0.28$, $P<0.001$). CE MRI were significantly correlated with ESR level ($r=0.44$, $P=0.001$) and VAS pain score of patients ($r=0.22$, $P=0.02$). No publication bias was detected.

CONCLUSION: Both NCE and CE MRI evaluation of knee synovitis in osteoarthritis were significantly correlated with macroscopic and microscopic features of synovial membrane. The higher correlation of CE MRI with microscopic histology compared NCE MRI approached but not reached significance.

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DISCLOSURE STATEMENT: F. Roemer is Shareholder of BICL, LLC. A. Guermazi is Shareholder of BICL, LLC and Consultant to Pfizer, TissueGene, OrthoTrophix, AstraZeneca, Sanofi, GE Healthcare and MerckSerono
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OPEN MRI ASSESSMENT OF INTRUSION IN FEMOROACETABULAR IMPINGEMENT

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INTRODUCTION: The most widely used quantifiers of femoroacetabular impingement (FAI) morphology are the alpha angle (a measure of femoral head asphericity) and beta angle (the clearance between the femoral neck and the acetabular margin), where a negative beta angle is an indicator of intrusion. These angles are measured on plain x-rays or an MRI slice through the middle of the femoral head that is normal to the coronal plane and contains the femoral neck axis. However, these readings do not allow precise localization of FAI pathology in three dimensions (3D) or provide information on the span of intrusion around the circumference of the femoral neck which is of particular interest in the surgical planning of FAI.

OBJECTIVE: Our objective was to investigate the correlations between the magnitude of beta angle, the intrusion span and the alpha angle associated with the highest intrusion in FAI and healthy populations in the clinically relevant supine FADIR (Flexion, Adduction, Internal Rotation) pose.

METHODS: Under the approval of our institutional research ethics board, twenty eight participants, ages 20-50, were recruited and classified into FAI (21 participants) and control (7 participants) groups based on x-ray scans. Each participant was scanned in a 0.5 Tesla upright MR scanner (MR Open, Paramed, Italy) with a T1-weighted gradient echo sequence with TR/TE=942.5/12ms, a slice thickness of 2.5 mm with a gap of 0.5 mm, FOV 250 mm, scan matrix 256*192, 34 slices, and imaging time 6 min 7 sec. Participants were scanned in a supine FADIR position which is used to assess impingement. Models of each participant's hip were reconstructed by manual segmentation. From these models, twenty four radial reformats with 15 intervals around the femoral-neck axis were generated in Matlab. Two independent readers determined alpha angle and beta angle in each plane, using the circle of best fit around the premier of femoral head in each plane and the axis of femoral neck axis. We determined inter-observer reliability using intraclass correlation coefficient. In each plane we reported the minimum beta angle, its corresponding location, and the alpha angle. We defined intrusion span as the number of slices with negative beta, multiplied by 15. We pooled the reading from all participants and performed spearman correlation to assess the correlation among pairs of reported variables. Mean values ± STD of alpha and beta angles in each plane were recorded for the two groups. Student's t-test was applied to test the difference between the two groups.

RESULTS: We found a moderately strong correlation between the alpha angle and intrusion span ($r=0.48$, $p=0.0306$). Compared to controls, the patient group on average had a higher alpha angle in all regions. In the anterior region, the beta angle was found to be significantly different between the patient, $-1°\pm26.9°$, and the control group $27.8°\pm43.1°$ ($p=0.0400$). The patient group revealed a strong correlation between the minimum beta angle and intrusion span ($r=0.72$, $p=0.00003$), and alpha angle ($r=0.77$, $p=0.0001$). Intraclass correlation coefficient for alpha and beta angle were found to be 0.87 and 0.93, respectively.

CONCLUSION: We have found that in a supine FADIR position, larger span deformities strongly correlate with more extensive intrusions (larger magnitude for negative beta angle). These findings are particularly useful in clinically relevant poses used intra-operatively to estimate the amount of burring required to restore a normal range of motion.

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BMD AND TEXTURE PARAMETER ANALYSIS OF TIBIAL SUBCHONDRAL BONE IN LOCATIONS COVERED AND NOT COVERED BY THE MENISCUS

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INTRODUCTION: A micro-CT study in normal human cadaveric knees showed that subchondral bone structure of the tibial plateau varied with location [1]. Particularly, sections covered by the meniscus (CM) showed that cartilage and subchondral bone plate were thinner and BV/TV, Tb.N, Tb.Th were lower compared to locations not covered by the meniscus (nCM).

OBJECTIVE: This study evaluates the effect of meniscal coverage on BMD and texture parameters in tibial subchondral bone.

METHODS: Clinical whole-body CT scans of 79 OA patients (age 64.5±11.0, KLG 2-3) were analyzed using MIAF-Knee. The subchondral-epiphyseal VOI, which covers the proximal third of the tibial epiphysis was divided into medial and lateral compartments. These were further divided into anterior, mid and posterior subVOIs. All subVOIs were divided into CM and nCM VOIs. For all resulting VOIs, BMD, global inhomogeneity and anisotropy were measured. Anisotropy measures the gray value directedness in a 26 neighborhood. Global inhomogeneity measures variations in gray value fluctuations in a VOI.

RESULTS: In the medial and lateral VOIs significant differences were observed between CM and nCM VOIs. For all VOIs BMD and inhomogeneity are significantly higher in regions not covered by meniscus, while anisotropy is significantly lower. Mid and posterior VOIs showed higher BMD and inhomogeneity than the anterior VOIs. Posterior the highest differences between CM and nCM VOIS were observed.

Medial	Total		Anterior		Mid		Posterior	
	CM	nCM	CM	nCM	CM	nCM	CM	nCM
BMD	220±49	348±74	176±51	243±66	312±95	391±87	242±66	399±112
Inhomogeneity	215±28	269±42	200±29	225±34	233±37	276±46	199±36	251±51
Anisotropy	74.5±1.3	73.1±1.6	74.3±1.5	73.4±1.6	73.7±1.8	72.7±1.8	75.0±1.4	73.0±2.0
Lateral	Total		Anterior		Mid		Posterior	
	CM	nCM	CM	nCM	CM	nCM	CM	nCM
BMD	188±39	242±60	143±46	165±54	213±53	255±71	216±52	308±91
Inhomogeneity	181±23	212±34	172±18	193±30	165±28	208±36	180±31	208±37
Anisotropy	74.7±1.4	73.9±1.6	74.5±1.7	73.7±1.7	74.6±1.7	73.8±1.7	74.7±1.5	73.7±1.7

Table: Mean values and standard deviations for all evaluated VOIs are shown. All differences between CM and nCM VOIs are significant (confirmed by two sided paired t-tests ($p<0.05$)).

CONCLUSION: Results show that BMD and texture of subchondral bone varies significantly depending on meniscal coverage and location in the epiphysis. This confirms the results of the mentioned micro CT study.

REFERENCES: [1] Touraine S, et al. PLoS ONE. 2017

SPONSOR: None
DICLOSURE STATEMENT: None
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