# Wednesday Sept 9

15:30 - 16:00 Registration & Snacks
PMU, Strubergasse 21, Entree House A (Ground Floor)

16:00-16:15 Welcome
Univ. Prof. Dr. med Wolfgang Sperl; Rector, Paracelsus Medical University
Univ. Prof. Dr. med. Jan Pruszak, Chair, Institute of Anatomy & Cell Biology, Paracelsus Medical University
Univ. Prof. Dr. med. Ali Guermazi, President ISOAI
Univ. Prof. Dr. med. Felix Eckstein, Organizer IWOAI 2020

16:15-17:00 **Session 1: Symptom-Imaging**
**Invited Lecture: Frank Roemer**
Clinical Outcomes & Translation of Structure Modification to Clinical Benefit

17:00-17:30 1-Tobias Hafner: Effects of collagenase exposure on cartilage functionality – A multiparametric quantitative MRI study (SO)
2-Victoria Racher: Dependence of WOMAC pain on radiographic knee OA status, age, sex, body mass index (BMI), race and contralateral knee pain status (SO)

17:30-18:00 Coffee Break

18:00-18:45 **Invited Lecture: Dirk Strunk**
Stem Cell Therapy - General Principles and Application to Osteoarthritis

19:00 Dinner: TRUMEREI (Strubergasse 26)

# Thursday September 10

9:00-9:45 **Session 2: Structure Modification**
**Invited Lecture: Hans Guehring**
Oral Design of Clinical Trials on Structure Modification - Lessons Learned from Sprifermin & Other Programs

9:45-10:45 3-Felix Eckstein: Long-term efficacy and safety of intra-articular Sprifermin in patients with knee osteoarthritis: Results from the 5-year FORWARD study (LO)
4-Henri Deckx: Study design of Roccella: A phase 2 clinical trial with disease-modifying osteoarthritis drug candidate GLPG1972/S201086 (SO)
5-Frank Roemer: Patterns of structural progression differ between Kellgren-Lawrence 2 and 3 knees fulfilling different definitions of a cartilage-meniscus phenotype (SO)

10:45-11:15 Coffee Break

11:15-12:00 **Session 3: Image Acquisition**
**Invited Lecture: Neal Bangerter**
Design of Novel Image Acquisition Approaches - Current Experience with 7 Tesla

12:00-13:00 6-Daniel Abrar: Detection of early cartilage degeneration in the tibiotalar joint using 3T GAGCEST imaging: A feasibility study (SO)
7-David Fuerst: Superficial cartilage transverse relaxation time (T2) predicts osteoarthritis disease progression – Data from the FNIH Biomarker study of the OAI (SO)
8- Marloes van Mourik: Accuracy of bone density and morphology measurements obtained from high resolution peripheral quantitative CT scans of the knee (SO)

9- Melissa Bevers: The healing of conservatively treated scaphoid fractures assessed by high-resolution peripheral quantitative computed tomography (Poster)

13:00-14:00 Lunch: Entree House A (Ground Floor)

14:00-14:45 **Session 4: Symptom Modification**
**Invited Lecture: Christine West**
Design of Clinical Trials on Symptom Modification - Lessons Learned from Anti-NGF Programs

14:45-15:30 10-Frank Roemer: Evolution of MRI-defined structural damage after anterior cruciate ligament injury over 5 years: The Kanon study (LO)
11-Peter Mandl: Tendon involvement and its role in hand function and pain in patients with osteoarthritis of the hand (SO)

15:30-16:00 Coffee Break

16:00-18:00 **Session 5: Poster Viewing** (Multifunction-Room Souterrain)

18:30 Dinner: SEMPRE (Strubergasse 28)

# Friday September 11

9:00-9:45 **Session 6: Image Segmentation**
**Invited Lecture: Akshay Chaudhari**
Novel Image Segmentation Approaches - Lessons Learned from Deep Learning Designs

9:45-11:00 12-Wolfgang Wirth: A deep learning automated segmentation algorithm accurately detects differences in longitudinal cartilage thickness loss – Data from the FNIH biomarkers study of the OAI (LO)
13-David Fuerst: 3D contour registration reveals that location-independent cartilage thickness scores and regional patterns differ between early and late follow-up after ACL rupture (SO)
14-Jana Kemnitz: Automated measurement of local, MRI-based measures of thigh adipose and muscle tissue are highly responsive to bidirectional change in body weight – Data from the OAI (SO)
15-Justus Schock: Artificial intelligence-based automated analysis of alignment in full-leg radiographs (SO)

11:00-11:30 Coffee Break

11:30-12:15 **Session 7: Mechano-Imaging**
**Invited Lecture: Anna-Maria Liphardt**
Mechano-Imaging - Imaging Application to Space Flight

12:15-13:15 16-Ali Guermazi: Frequency of osteoarthritis in athletes undergoing MRI at the Olympics in Rio 2016 (LO)
17-Tobias Hafner: Biomechanical Imaging of Proteoglycan-depleted human articular cartilage – A functional MRI study (SO)
18-Rafael Heiss: Effects of sports climbing on cartilage structural composition of the metacarpo-phalangeal and proximal interphalangeal joints as assessed by T2 relaxometry at 7T MRI (SO)

13:15-14:15 Lunch: Entree House A (Ground Floor)

14:15-15:45 **Session 8: Podium Discussion**

15:45-15:55 Edwin Oei: Invitation to 15th IWOAI 2021 in Rotterdam, The Netherlands

15:55-16:00 Closing Note: Felix Eckstein & Ali Guermazi

16:00 Drinks: Entree House A & TRUMMEREI

19:00 Dinner: Hangar 7 Bar

# Saturday September 12

9:00 Post Conference Tour 1: Bad Reichenhall (Easy: Predigtstuhl, Schlegelmulde)

# Sunday September 13

8:00 Post Conference Tour 2: Berchtesgaden (Challenging: Watzmann [-haus])

# Covid-19 - Safety concept

**for events at the Paracelsus Medical University**
**(as of July 2020)**

PARACELSUS
MEDIZINISCHE PRIVATUNIVERSITÄT

We would like to make your visit at our university as pleasant and safe as possible. For this purpose, the following measures and regulations shall apply:

**Participation in the event:**
Visitors are requested to read the hygiene guidelines carefully in advance and to follow them meticulously. Persons with symptoms, who had contact with COVID-19-positive people and/or quarantine notification are asked to refrain from attending an event.

**Entrance and exit:**
Entrances and exits are clearly marked as such.
Dispensers for hand disinfection are available in all entrance areas and signs with rules of conduct.
Visitors are requested to pass the entrances and exits at a suitable distance from each other. In order to better regulate the flow of visitors, it is recommended to allocate timeslots.
In the common areas (corridors + foyers), it is required to wear mouth/nose protec-tion if the minimum distance of 1 m cannot be maintained.

**Event and lecture halls:**
Seats in the event and lecture halls are numbered and are at least 1.2 m apart. While the visitors are in their assigned seats, they do not have to wear protective masks.
The lectern is equipped with a Plexiglas screen to retain any aerosol particles that may be emitted by the speaker. Microphones and headsets are disinfected prior to every use and must not be used by several people at the same time.

**Documentation:**
Every conference participant has to fill in a form with personal contact data, in-formation about the duration of his/her stay and room/seat number and shall pro-vide this form to the university. These data are only used for the quick identification of infection chains in case of COVID-19 spreading. They will be made available ex-clusively to the health authorities upon request, kept in safe custody for a maximum of one month and then destroyed.

**Break & Catering:**
Protective masks must be worn in all common areas (corridors, foyers, toilets) if the minimum distance of 1 m cannot be maintained.
Catering with an open buffet for self-service is not permitted. Lunchboxes, pack-aged food and drinks for self-service are permitted, as are buffet stations where catering staff serve the food.

**Cleaning /Hygiene:**
All guests are requested to contribute to a higher standard of hygiene themselves by washing their hands regularly, by refraining from shaking hands and hugs and by not coughing or sneezing into the air.
All rooms as well as the furniture used are thoroughly cleaned before and after each event, and the surfaces that are touched - such as door handles, light switches, lift buttons etc. - are disinfected.

# ORAL PRESENTATIONS

**EFFECTS OF COLLAGENASE EXPOSURE ON CARTILAGE FUNCTIONALITY – A MULTIPARAMETRIC QUANTITATIVE MAGNETIC RESONANCE IMAGING STUDY**

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INTRODUCTION: Cartilage functionality is determined by tissue structure and composition as well as the complex interplay of its fluid and solid constituents during loading and relaxation. If tissue structure and/or composition are altered, the tissue is predisposed to premature degeneration and osteoarthritis.

OBJECTIVE: As the imaging correlates of cartilage functionality remain to be defined, the aim of this study was to evaluate the dose-dependent effects of collagenase exposure, i.e. primarily collagen disruption and secondarily proteoglycan depletion, on the response to loading as assessed by serial multiparametric quantitative Magnetic Resonance Imaging (qMRI). Our hypotheses were that collagenase exposure significantly and dose-dependently alters cartilage structure and composition as controlled by histology and that these alterations were quantitatively reflected by significant pre- and post-exposure differences in the T1, T1ρ, T2, and T2* maps.

METHODS: In total, macroscopically intact 30 human lateral femoral osteochondral samples obtained from total knee arthroplasties underwent serial T1 (inversion recovery), T1ρ (spin-lock multigradient echo), T2 (multi-spin echo), and T2* (multi-gradient echo) mapping on a clinical 3.0 T MRI scanner (Achieva, Philips) in the unloaded reference configuration ($\delta_0$) and under moderate (15.1 N, $\delta_1$) and strong indentation loading (28.6 N, $\delta_2$) using a pressure-controlled quasi-static loading device. Serial T1, T1ρ, T2, and T2* mapping was performed before and after exposure to either low concentration (LC, 0.5 mg/mL, n=10) or high concentration (HC, 1.5 mg/mL, n=10) of collagenase. Untreated samples served as controls (n=10). Loading responses were determined for the entire sample and the directly loaded (i.e. sub-pistonal) and bilaterally adjacent (i.e. peri-pistonal) tissue regions, quantified as relative changes, and analysed using adequate parametric and non-parametric statistical tests. Histological evaluation served as reference.

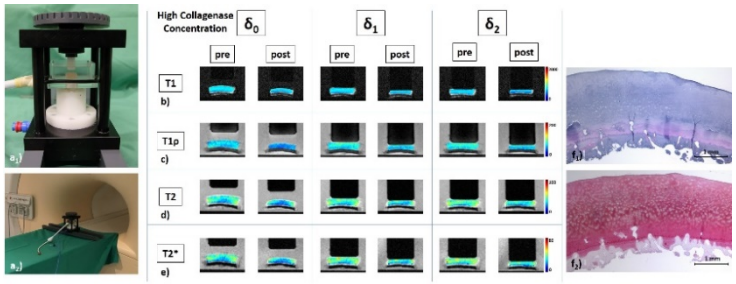


**Figure 1:** Details of experimental setup (a), images of an exemplary high-concentration collagenase-treated cartilage sample and its response to loading (b-e), and corresponding histological sections (f). An MRI-compatible pressure-controlled indentation loading device was used to load cartilage in a standardized manner (a). Serial quantitative T1 (b), T1ρ (c), T2 (d), and T2* (e) maps as well as corresponding histological sections (f, HE staining [$f_1$], Saf O staining [$f_2$]) of a representative cartilage sample before and after exposure to high concentration of collagenase type II at 1.5 mg/mL.

RESULTS: Histologically, dose-dependent reductions in cartilage thickness, surface disintegration, loss of tissue substance, and proteoglycans were observed. Pre- and post-exposure response-to-loading patterns revealed distinctly different intra-tissue adaptations in all qMRI parameters that were related to loading intensity and collagenase concentration. While T1 generally decreased with loading, regardless of collagenase exposure, T1ρ increased significantly after HC exposure (p=0.008). Loading-induced increases in T2 were significantly different from corresponding decreases after LC exposure (p=0.006). Loading-induced changes in T2* were ambiguous.

CONCLUSION: Aberrant loading-induced changes in T2 and T1ρ seem to reflect moderate and severe matrix changes, respectively, and indicate the close interrelatedness of matrix changes and functionality in cartilage.

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DISCLOSURE STATEMENT: None.
ACKNOWLEDGEMENT: None.
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**DEPENDENCE OF WOMAC PAIN ON RADIOGRAPHIC KNEE OA STATUS, AGE, SEX, BODY MASS INDEX (BMI), RACE, AND CONTRALATERAL KNEE PAIN STATUS**

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INTRODUCTION: It has been proposed that structural (e.g. radiographic) change and symptoms are highly discordant in knee osteoarthritis, although work comparing radiographic alterations with symptoms between both knees in the same patient (between knee, within-person analysis) have revealed a stronger relationship.

OBJECTIVE: We analyze the impact of age, sex, body mass index (BMI), race, and contra-lateral knee pain status on the level of knee pain perception, adjusting for radiographic status.

METHODS: We used data from 4171 participants of the OAI who had complete information on the above measures at the 12-month follow-up time point. Probabilistic Index Models (PIMs) were used due to the ordinal scale of the outcome variable WOMAC pain score and the study design. The target knee was defined as the knee with the more severe WOMAC pain score, with contralateral knee pain status being included in the model. The PIM quantifies the impact of potential prognostic variables on the so-called probabilistic index. The corresponding effect measure is typically referred to as "non-parametric relative effect" and can be interpreted as the probability that a random subject, with the covariate value of interest, scores higher on the WOMAC pain score than a random subject without the characteristic of interest. We defined 5 categorical groups with increasing radiographic severity that were defined based on the KLG, and on the maximum medial or lateral radiographic JSN grade (v1.8 of the central OAI radiographic readings): Group 1: non-ROA (n=1857); Group 2: definite ROA without JSN (n=427); Group 3: definite ROA with mild JSN (n=927); Group 4: definite ROA with moderate JSN (n=679); Group 5: definite ROA with serve JSN (n=285). In addition, we conducted a sensitivity analysis and applied backward variable elimination based on the Akaike Information Criterion, using a logistic regression model with the outcome variable WOMAC pain score "yes (>0) /no (=0)". All p-values were adjusted for multiplicity using the Bonferroni procedure.

RESULTS: The logistic regression model revealed a statistically significant impact of ROA group, sex and BMI on WOMAC pain that also was significant in the PIM. Therefore, ROA group, sex and BMI were considered in the final PIM. In the latter, pairwise comparisons between the 5 groups yielded highly significant effects on WOMAC pain scores for 9 of the 10 comparisons (Table 1). Only the comparison between groups 2 and 3 was not statistically significant at the familywise level alpha=0.01 (relative effect=0.47, 99% confidence interval (CI) = [0.43,0.52]; p=0.82). The largest effect for any difference between groups in ROA severity was detected between groups 4 and 5 (relative effect=0.65). The PIM also confirmed that a higher BMI and female sex were associated with higher WOMAC pain score (with adjustment for radiographic severity), with relative effects of 0.51 (CI=[0.51,0.51]; p<2.40e-15) and 0.57 (CI=[0.54,0.59]; p=1.83e-12), respectively.

| | ROA gr. 1 | ROA gr. 2 | ROA gr. 3 | ROA gr. 4 | ROA gr. 5 |
|---|---|---|---|---|---|
| ROA gr. 1 | | 0.60 | 0.58 | 0.68 | 0.80 |
| ROA gr. 2 | 5.80e-11 | | 0.47 | 0.59 | 0.73 |
| ROA gr. 3 | 2.12e-09 | 0.82 | | 0.62 | 0.75 |
| ROA gr. 4 | <2.40e-15 | 0.81e-05 | 1.44e-13 | | 0.65 |
| ROA gr. 5 | <2.40e-15 | <2.40e-15 | <2.40e-15 | 5.40e-14 | |

**Table 1.** p-values (below diagonal) and effect sizes (above diagonal) of pairwise comparison of structure groups

CONCLUSION: It is not surprising that ROA severity showed a strong relationship with WOMAC pain. However, it is interesting that the only radiographic increment that did not differ significantly was that from definite ROA without to definite ROA with mild (grade 1) JSN. This may be explained by the uncertainty of accurately identifying mild JSN on a radiograph. The largest effect for any between-group difference in ROA severity was detected between ROA group 4 and 5, suggesting that JSN grade 3 (bone-to bone contact) is a highly important structural correlate of knee pain.

SPONSOR: None
DICLOSURE STATEMENT: see affiliations FE has consulted for Merck, Bioclinica, Servier, Samumed, Roche, Kolon Tissuegene, Galapagos, Novartis and ICM.
ACKNOWLEDGMENT: The OAI participants, OAI site investigators, coordinating center and funders
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**LONG-TERM EFFICACY AND SAFETY OF INTRA-ARTICULAR SPRIFERMIN IN PATIENTS WITH KNEE OSTEOARTHRITIS: RESULTS FROM THE 5-YEAR FORWARD STUDY**

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INTRODUCTION: The 5-year Phase II FORWARD study assessed the efficacy and safety of the potential disease-modifying osteoarthritis drug (DMOAD) sprifermin (recombinant human fibroblast growth factor 18) in patients with symptomatic, radiographic knee osteoarthritis (OA).

OBJECTIVE: To report the long-term 5-year efficacy and safety results of FORWARD. To explore whether translation of structure modification to a symptomatic benefit, previously observed in a "subgroup at risk" (SAR) at 3-year follow-up, is maintained longer term.

METHODS: Patients were randomized 1:1:1:1:1 to intra-articular sprifermin 100 or 30 µg q6mo, 100 or 30 µg q12mo, or placebo (PBO), for 18 months. The treatment period-related analysis for the primary endpoint was at Year 2, with an extended 3-year observation period. The intent-to-treat (ITT) population included all randomized patients; the modified (m)ITT population included all patients with a baseline and ≥1 qMRI reading up to Year 2. Post-hoc exploratory analysis was conducted in a "subgroup at risk" (SAR, n=161), with minimum medial or lateral JSW of 1.5–3.5mm and WOMAC pain 40–90 at baseline. Treatment differences vs placebo were estimated using a repeated measures model controlling for baseline, treatment, time, pooled country and treatment by time interaction. Confidence intervals (CIs) were adjusted for multiplicity of treatments using Dunnett adjustment. Linear dose-effect trend tests were performed exploratively at each timepoint.

RESULTS: 474 (86.3%) patients completed the primary 2-year observation period; 442 (80.5%) and 378 (69%) patients completed the 3- and 5-year extended follow-up periods, respectively. The significant dose-response effect of sprifermin on longitudinal change in total femorotibial joint (TFTJ) cartilage thickness (trend test, $p<0.001$), and the 0.05 mm mean increase in TFTJ cartilage thickness with sprifermin 100 µg q6mo (highest dose) vs placebo (95% CI 0.004, 0.095; $p=0.015$) observed at Year 2 were sustained to Year 5. WOMAC pain scores improved by ~50% from baseline to Year 5 in all cohorts, including placebo. Post-hoc analysis of the SAR identified a differentiation in WOMAC pain scores between the sprifermin 100 µg q6mo and placebo groups at Year 2 (-5.82; 95% CI -18.87, 7.23), Year 3 (-8.75; 95% CI -22.42, 4.92) and Year 5 (-10.08; 95% CI -25.68, 5.53). Adverse events (AEs) were mostly moderate in severity. 181 patients (33%) reported serious AEs, none of which were deemed related to treatment. AE-related study withdrawals were <10%, the majority of which were musculoskeletal and soft tissue disorders. At Year 5, there was no notable difference in the incidence of adverse events (AEs), serious AEs or study discontinuation due to AEs in any sprifermin group vs placebo.

CONCLUSION: In the longest duration DMOAD study reported to date, FORWARD, sprifermin maintained long-term structural modification of articular cartilage vs placebo despite a 3.5-year treatment-free period (between the last intra-articular injection at 18 months, and the last follow-up time point at 60 months), with no new safety signals being observed. Pain improvement vs placebo was sustained between year 3 and year 5 in a "subgroup at risk" (SAR) of structural and symptomatic progression. This suggests potential disease modification with sprifermin, with delayed knee OA structural progression and translation of structural modification to clinical benefit. It also identifies a potential target dose and patient population for future Phase III trials.

SPONSOR: Merck KGaA, Darmstadt, Germany
DICLOSURE STATEMENT: Employment status as provided in the affiliations. FE consults for Merck KGaA, Bioclinica, Samumed, Kolon-Tissuegene, Servier, Galapagos, Roche, Novartis and ICM.
ACKNOWLEDGMENT: We thank the FORWARD patients and investigators for their invaluable contributions to the success of this study, and Bioscript for help in preparing the abstract text.
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**STUDY DESIGN OF ROCCELLA: A PHASE 2 CLINICAL TRIAL WITH DISEASE-MODIFYING OSTEOARTHRITIS DRUG CANDIDATE GLPG1972/S201086**

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INTRODUCTION**:**
Loss of articular cartilage is one of the major signs of osteoarthritis (OA). Aggrecan, the main proteoglycan component of the extracellular matrix of articular cartilage, is cleaved by ADAMTS-5 (A Disintegrin And Metalloproteinase with ThromboSpondin-motif-5). GLPG1972/S201086, a potent and highly selective inhibitor of ADAMTS-5, is an oral Disease-Modifying OA Drug (DMOAD) candidate that was shown to be well tolerated in phase 1 studies.

OBJECTIVE: To present the study design of ROCCELLA, a large phase 2 clinical trial in patients with knee OA (KOA), evaluating the efficacy of GLPG1972/S201086 in reducing cartilage loss, as well as safety outcomes.

METHODS: ROCCELLA is a multinational 52-week, multicentre, randomized, double-blind placebo-controlled, dose-ranging phase 2 trial in KOA patients (NCT03595618). Eligible patients were aged 40–75 years with a diagnosis of primary femorotibial KOA, a pain score of 40–90mm on a 100 mm Visual Analogue Scale (VAS), predominant medial disease and a combined Kellgren/Lawrence (KL) grade of 2 or 3 and OARSI JSN grade of 1 or 2 upon central reading of the X-ray. If both knees were eligible, the target knee was selected based first on the highest KL grade, then on the highest JSN grade and finally on the highest pain VAS score at baseline. Patients were randomized 1:1:1:1 to take placebo or one of three dose levels of GLPG1972/S201086 orally once daily for 52 weeks. Evaluation of the target knee was carried out by qMRI at baseline, week 28 and week 52, or at early withdrawal. The primary endpoint of the study is change in cartilage thickness of the central medial tibio-femoral compartment (cMTFC) of the target knee from baseline to week 52. Secondary endpoints are safety and tolerability and changes from baseline in the target knee of cartilage thickness in areas other than the cMFTC and bone area around the knee on qMRI, KOA "progressor" rates, Joint Space Width on X-ray, pain VAS, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total and sub scores, Patient Global Assessment VAS and the proportion of Outcome Measures in Rheumatology (OMERACT)-OARSI responders. A Mixed-effects Model for Repeated Measures will be used for the primary analysis. The randomisation was stratified by geographic region.

RESULTS: The study started in August 2018 and was fully recruited by June 2019. Large numbers of patients with KOA had to be screened to meet the stringent pre-specified selection criteria. The study completion is expected by end of 2020.

CONCLUSION: This is the first large phase 2 study where patients with primary KOA are treated for 52 weeks with GLPG1972/S201086, an orally administered DMOAD candidate. This clinical trial was designed with a combination of two radiological selection criteria to ensure sufficient structural progression (cartilage loss) in the study population.

SPONSOR: This study was funded by the Institut de Recherches Internationales Servier (Suresnes, France) and Galapagos NV (Mechelen, Belgium).
DICLOSURE STATEMENT: H. Deckx, E. van der Aar, M. Van der Stoep and M. Wooning are employees of Galapagos NV. K. Bernard., S. Grankov., O. Imbert., and M. Pueyo are employees of Institut de Recherches Internationales Servier. F.Eckstein is co-owner and employee of Chondrometrics and has received consulting fees from: Merck, Bioclinica, Servier, Samumed, Roche, Kolon Tissuegene, Galapagos, Novartis and ICM.
ACKNOWLEDGMENT: Editorial support was provided by Oxford PharmaGenesis and funded by Galapagos NV.
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**PATTERNS OF STRUCTRAL PROGRESSION DIFFER BETWEEN KELLGREN-LAWRENCE 2 AND 3 KNEES FULFILLING DIFFERENT DEFINITIONS OF A CARTILAGE-MENISCUS PHENOTYPE**

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**Friedrich-Alexander Univ. Erlangen-Nürnberg (FAU) and Universitätsklinikum Erlangen, Erlangen, Germany
***Orthopaedics and Arthritis Center of Outcomes Research, BWH, Harvard Medical School, Boston, MA, USA

INTRODUCTION: Imaging plays an important role in defining structural disease severity and potential suitability of patients recruited to disease-modifying osteoarthritis drug (DMOAD) trials. Three main structural phenotypes in knee OA have been proposed, i.e., inflammation, cartilage-meniscus and subchondral bone. Recently, Rapid OsteoArthritis MRI Eligibility Score (ROAMES[1]) system has been introduced that allows structural phenotypic stratification based on abbreviated MRI assessment and thus, may potentially be applicable in screening efforts for inclusion into clinical DMOAD trials. The cartilage-meniscus phenotype has received particular attention as such knees are likely to benefit most from pharmacological intervention. However, cartilage damage that is too severe may be of negative impact.

OBJECTIVE: To describe frequencies for different structural thresholds regarding the definition of a modified ROAMES cartilage-meniscus phenotype and to report patterns of progression in Kellgren-Lawrence (KL) 2 and 3 knees with different cartilage-meniscus phenotypes over 48 months in the Foundation for National Institutes of Health (FNIH) Osteoarthritis Biomarkers Consortium cohort, a well-defined subsample of the larger Osteoarthritis Initiative (OAI) study comparable to a clinical trial population.

METHODS: The study sample from the FNIH project was selected as a nested case-control study with knees showing either 1) radiographic and pain progression (i.e., "composite" cases), 2) radiographic progression only, 3) pain progression only, and 4) neither radiographic nor pain progression at 48 months. In this study the composite and JSL only cases were defined as the outcome of interest. MRI was performed on 3T systems. MRIs were read according to the MOAKS scoring system. Knees were stratified into different cartilage-meniscus and phenotypes using the baseline visits. The current analysis focuses on the medial compartment, which is commonly the primary outcome in clinical DMOAD trials. Three different phenotypes were defined according to the maximum severity of cartilage damage in the medial compartment: 1) $\leq 2.2$ (10-75% of region of cartilage surface area with 10-75% affected by full thickness loss) in any of 5 subregions, i.e. 'D1' 2) $\leq 2.1$ (10-75% of region of cartilage surface area with <10% affected by full thickness loss), i.e. 'D2' and 3) $\leq 2.0$ (10-75% of region of cartilage surface area without full thickness loss), i.e. 'D3'. Cartilage status in the lateral compartment and meniscal status was not considered. The relation of each of these definition to odds of being in the composite case or JSL only group compared to those not having that phenotype was determined using logistic regression. Sensitivity analyses focused on the reference knees not fulfilling these phenotypic definitions to understand proportions of knees with either "too much" (cartilage damage above threshold including all grade 3 lesions) or "no" damage (5 medial TF subregions scored as 0).

RESULTS: After exclusion of KL 1 knees (n=71) and knees with posterior meniscal root tears (n=44), 485 knees were included. Excluded participants were similar to included participants with respect to baseline characteristics and case status (20% of composite cases excluded vs. 19% of controls). Mean age of the participants was 61 years (SD ± 8.8), 59 % of the participants were women, average BMI was 31.0 kg/m$^2$ (SD ± 4.8). 297 knees were KL 2 and 188 knees KL 3. For KL2 knees 191(64%) knees fulfilled D1 criteria, 183 (62%) D2 and 167 (56%) D3. For KL3 these numbers were 164 (87%) for D1, 103 (55%) for D2 and 77 (41%) for D3. Odds for being a composite case were 2.52 (95% CI 1.40,4.54) for D1, 1.93 (95% CI 1.11,3.35) for D2 and 1.92 (1.13,3.28) for KL2 knees. For KL3 knees odds were 0.32 (95% CI 0.13,0.78) for D1, 0.56 (95% CI 0.31,1.01) for D2 and 0.49 (95% CI 0.26,0.91) for D3. For the JSL only outcome numbers were similar with increased odds for KL2 knees and a protective effect seen for KL3 knees. For KL2 2% (D1), 4% (D2) and 10% (D3) of the controls had too much damage, while 34% did not have any damage. For KL3 12%, 45% and 59% had too much damage, while only one (1%) knee had no damage in the medial compartment.

CONCLUSION:
Phenotypic stratification of the cartilage-meniscus phenotype in different subtypes is feasible and may help in defining trial cohorts at screening. Increased odds for progression are seen for KL2 knees and all definitions, while a seemingly protective effect is seen for KL3 knees. The latter can be explained by the fact that KL3 knees stratified by the suggested definitions have comparably mild cartilage damage at screening. 1/3 of KL2 knees do not have medial cartilage damage, which is an important finding and needs to be considered when selecting patients for clinical trials based on X-ray assessment only.

RERFERENCE: Roemer FW et al. Osteoarthritis Cartilage 2020;28(1):71-81.
DICLOSURE STATEMENT: Dr. Guermazi is consultant to Merck Serono, AstraZeneca, Pfizer, Roche, Galapagos, and TissuGene and is shareholder of BICL, LLC. Dr. Roemer is shareholder of BICL, LLC. Dr. Roemer is consultant to Calibr. Dr. Collins is consultant to BICL.
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**DETECTION OF EARLY CARTILAGE DEGENERATION IN THE TIBIOTALAR JOINT USING 3T GAGCEST IMAGING: A FEASIBILITY STUDY**

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INTRODUCTION: Glycosaminoglycan chemical exchange saturation transfer (gagCEST) imaging is a compositional magnetic resonance imaging (MRI) technique that does not rely on the intravenous administration of gadolinium-based contrast agents and has shown promising results at lumbar intervertebral disks. At smaller joints, such as the tibiotalar joint, research is sparse and so far limited to 7 Tesla (T) MRI systems.

OBJECTIVE: To establish and optimize a stable 3 Tesla (T) glycosaminoglycan chemical exchange saturation transfer (gagCEST) imaging protocol for assessing the articular cartilage of the tibiotalar joint in healthy volunteers and patients after a sustained injury to the ankle.

METHODS: Using Bloch-McConnell simulations, we optimized the sequence protocol for a 3 T MRI scanner for maximum gagCEST effect size within a clinically feasible time frame of less than 07.30 minutes. This protocol (with the following framework conditions: gradient-field strength= 0.8, pulse duration= 300 ms and number of pulses= 8) was then used to analyze the gagCEST effect of the articular cartilage of the tibiotalar joint of 17 healthy volunteers and five patients with osteochondral lesions (OLT) of the talus following ankle trauma. Reproducibility was tested with the intraclass correlation coefficient. For statistical analysis, a linear mixed model has been used.

RESULTS: The mean magnetization transfer ratio asymmetry (MTRasym), i.e. the gagCEST effect size, was significantly lower in patients than in healthy volunteers (0.34 ± 1.9 % vs. 1.49 ± 0.11 %; $p<0.001$). Intra- and inter-rater reproducibility was excellent with an average measure intraclass correlation coefficient (ICC) of 0.97 and a single measure ICC of 0.91 ($p<0.01$).

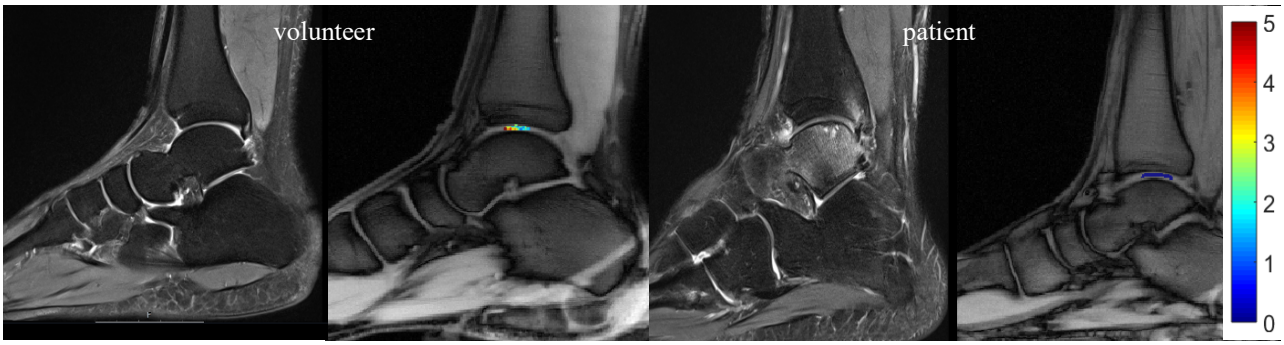


**Figure 1.** Sagittal proton-density weighted images and corresponding glycosaminoglycan chemical exchange saturation transfer (gagCEST) maps of a 29-year-old healthy male (volunteer) and an age-matched male patient with an established osteochondral lesion of the talus (OLT; patient). Tibiotalar joint cartilage of the healthy volunteer has higher gagCEST values than the patient (color-coded gagCEST maps overlaid onto T1w morphological image).

CONCLUSION: In this feasibility study, pre-morphological tibiotalar joint cartilage damage was quantitatively assessable on the basis of the optimized 3 T gagCEST imaging protocol that allowed stable quantification gagCEST effect sizes across a wide range of health and disease in clinically feasible acquisition times.

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**SUPERFICIAL CARTILAGE TRANSVERSE RELAXATION TIME (T2) PREDICTS OSTEOARTHRITIS DISEASE PROGRESSION – DATA FROM THE FNIH BIOMARKER STUDY OF THE OSTEOARTHRITIS INITIATIVE (OAI)**

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INTRODUCTION: MRI spin-spin (transverse) relaxation time (T2) has been proposed as an imaging biomarker for the detection of alterations in articular cartilage composition. T2 is thought to reflect collagen integrity, orientation, and hydration, with higher values indicating early cartilage damage. T2 was shown to be associated with cartilage histological grading and mechanical properties. However, whether cartilage T2 predicts disease progression in knees with established OA remains controversial. Furthermore, whether layer-specific (superficial vs. deep cartilage) T2 is associated with clinically relevant OA progression has not been examined in a large sample.

OBJECTIVE: To examine whether layer-specific cartilage T2, and/or change in T2 over 1 year predicts clinically relevant (radiographic, or symptomatic, or both) knee osteoarthritis (OA) disease progression.

METHODS: The OAI biomarker consortium was a nested case-control study on 600 Kellgren Lawrence grade 1-3 knees from 600 Osteoarthritis Initiative participants. Progressor knees had both medial tibiofemoral radiographic joint space width (JSW) loss (≥0.7 mm) and a persistent increase in WOMAC pain (≥9 on a 0-100 scale) at 24-48 month from baseline (n=194). Yet, multi-echo spin-echo (MESE) MRIs for cartilage T2 analysis were only acquired in right knees (97 progressor knees). These were compared to 104 right control knees without JSW or pain progression. 53 right knees had JSW progression, and 57 pain progression only. Previously published cartilage thickness segmentations obtained with a double echo steady stated (DESS) MRI sequence at baseline and 1 year later were matched (spatially registered) to non-segmented MESE images, to extract superficial and deep femorotibial cartilage T2. Superficial medial femorotibial compartment (MFTC) T2 at baseline was the primary, and longitudinal change in deep MFTC T2 between baseline and 12 months follow-up the secondary analytic outcome of this post-hoc exploratory study.

RESULTS: Baseline superficial (but not deep) MFTC T2 was significantly elevated in progressor (47.5 ms [95% confidence interval [CI] 46.8, 48.2]) vs non-progressor knees (45.8 ms [95% CI 45.0, 46.5]; $p<0.01$ unpaired t-test; Cohen's D=0.46). This difference remained significant (p=0.01) after adjustment for age, sex, BMI, WOMAC pain, and medial JSN grade (ANCOVA). Neither superficial nor deep layer 12-month change in T2 differed significantly between case and control knees.

CONCLUSION: Superficial, but not deep, cartilage T2, measured at one time point in the affected (medial) compartment, was able to predict subsequent, clinically relevant progression of knee OA. Longitudinal change in deep cartilage T2 over 1 year, however, failed to reach statistical significance.

SPONSOR: Ludwig Boltzmann Institute for Arthritis and Rehabilitation, Austria.
DICLOSURE STATEMENT: X.B. DF is a part time employee of Chondrometrics GmbH. WW and FE are part time employees and co-owners of Chondrometrics GmbH. WW has consulted for Galapagos. DJH Hunter has consulted for Merck Serono, Pfizer, Lilly and TLCBio. FE has consulted for Merck KGaA, Bioclinica, Samumed, Kolon-Tissuegene, Servier, Galapagos, Roche, Novartis and ICM.
ACKNOWLEDGMENT: The authors thank the expert readers at Chondrometrics GmbH for the segmentation of the DESS MRI data that were used to extract T2 in the current analysis. We particularly thank Dr. Susanne Maschek for quality control readings of the segmentations.
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**ACCURACY OF BONE DENSITY AND MORPHOLOGY MEASUREMENTS OBTAINED FROM HIGH RESOLUTION PERIPHERAL QUANTITATIVE CT SCANS OF THE KNEE**

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INTRODUCTION: High-Resolution peripheral Quantitative CT (HR-pQCT) is an imaging technique that can create 3D images of bone *in-vivo* at the distal radius/tibia at a resolution sufficient to resolve the trabecular bone structure and cortical porosity. Using the 2nd generation HR-pQCT scanner it now is possible as well to scan the knee region. As the size of the knee is much larger than that of the distal radius/tibia, we expected that beam hardening artefacts may affect the measured densities. Furthermore, as the structure of the bone near the subchondral region considerably differs from that of the radius/tibia, the accuracy of the morphology measures is not known

OBJECTIVE: To quantify the accuracy of HR-pQCT density and morphology measurements in the subchondral region of the tibia.

METHODS: Six human tibia plateaus obtained from patients that received total knee arthroplasty were collected. From each plateau four or five 8 mm cylindrical cores were drilled at prescribed positions (Fig. 1A). After drilling the cores were placed back in the tibia plateau (Fig. 1B) and a HR-pQCT (Scanco XtremeCT II) scan of the full plateau with cores was made in the clinical orientation at 61 microns resolution. Following, metal pins were glued at the bone cores and these were connected to a base plate that could position the individual cores *ex-situ* at the same location in the scanner field of view as when they were *in-situ* (Fig. 1C). Each of the cores then was scanned again with HR-pQCT. Finally, all cores were also scanned using micro-CT at 21 microns. The accuracy of the density measurement in-situ was quantified by comparing bone mineral density (BMD) measurement of the cores *in-situ* and *ex-situ*. The accuracy of the morphology measurements was quantified by comparing morphology parameters (volume fraction BV/TV, trabecular separation Tb.Sp, trabecular number Tb.N and trabecular thickness Tb.Th) measured from HR-pQCT images to those measured from micro-CT.

RESULTS: A significant mean difference in BMD of -6.9% (CI: -20.8 to 6.9%) was found for the cores scanned in-situ compared to the ex-situ case. The larger differences were found for cores with the higher densities. When comparing HR-pQCT and micro-CT measurements of the *ex-situ* cores, no significant differences were found for BMD, BV/TV and Tb.Sp, but Tb.N was significantly lower and Tb.Th was significantly higher in HR-pQCT images compared to micro-CT.

CONCLUSION: Beam hardening did have an effect on the density measurement, in particular for dense regions. However, when studying changes between patients or within patients, this error will be consistent and likely will not impact results. The underestimation of Tb.N and overestimation of Tb.Th indicates that some of the thinner trabeculae are lost when scanning the knee.

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**THE HEALING OF CONSERVATIVELY-TREATED SCAPHOID FRACTURES ASSESSED BY HIGH-RESOLUTION PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY**

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INTRODUCTION: The healing of a scaphoid fracture can be challenging. Adequate monitoring of fracture healing may improve clinical outcome but is limited with currently used imaging modalities.

OBJECTIVE: The aim of this study was to assess the healing of conservatively-treated scaphoid fractures at microarchitectural level with high-resolution peripheral quantitative computed tomography (HR-pQCT).

METHODS: HR-pQCT scans were acquired of the scaphoid bone of fourteen patients with a scaphoid fracture confirmed on HR-pQCT and treated with a cast. The scans were taken at baseline - within 10 days after initial presentation at the emergency department (ED) - and at three, six, twelve, and 26 weeks after initial presentation. They were analyzed to quantify bone mineral density, microarchitecture, and ultimate force. Linear mixed-effects models were used to evaluate longitudinal changes in the parameters.

RESULTS: Data of three patients were excluded due to absence of a scaphoid fracture and change to surgical treatment. In the remaining eleven patients, median time to cast removal was 6.6 (IQR: 4.3) weeks. In these patients, the fracture line was more apparent at three weeks after initial presentation than at baseline, and there was blurring of the fracture region at six and twelve weeks after initial presentation (see Fig.1). Small surface and trabecular disruptions were visible in some fractures at 26 weeks. Density, trabecular thickness, and ultimate force significantly decreased compared to baseline and showed a minimum at six weeks after initial presentation (-13.6%, -6.7%, and -23.7% compared to baseline, respectively). Thereafter, density stabilized and ultimate force increased and both remained significantly lower than baseline at twelve and 26 weeks after initial presentation. Trabecular thickness also increased after six weeks and remained significantly lower than baseline at twelve weeks. Trabecular number decreased to a minimum at 26 weeks (-7.9% compared to baseline) and was significantly lower than baseline at six, twelve, and 26 weeks. Trabecular separation was significantly higher than baseline at the same timepoints with a maximum at twelve weeks (+19.7% compared to baseline).

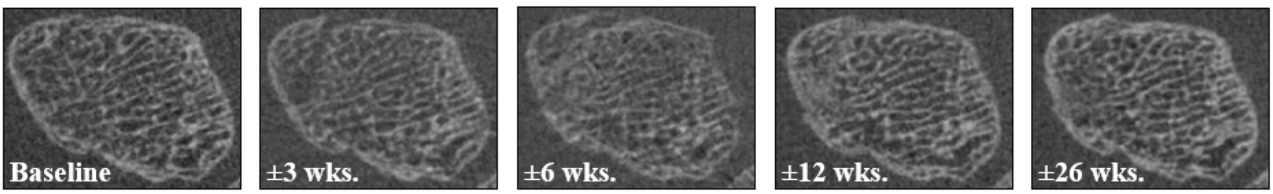


*Fig. 1: Slices of an HR-pQCT scan showing the healing of a scaphoid fracture until 26 wks. after initial presentation.*

CONCLUSION: The healing of conservatively-treated scaphoid fractures appears to start with a decrease in bone mineral density, trabecular thickness, and ultimate force until six weeks after initial presentation and a subsequent stabilization or increase. There appears no densitometric, microarchitectural, and bone biomechanical restoration to baseline yet at 26 weeks after initial presentation.

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DISCLOSURE STATEMENT: Bert van Rietbergen is an external consultant for Scanco Medical AG.
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**EVOLUTION OF MRI-DEFINED STRUCUTRAL DAMAGE AFTER ANTERIOR CRUCIATE LIGAMENT INJURY OVER 5 YEARS: THE KANON STUDY**

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INTRODUCTION: Anterior cruciate ligament (ACL) reconstruction is done to improve function of a mechanically unstable knee, and to prevent osteoarthritis. MRI has been used to describe the development of structural joint changes after ACL injury but no long-term data are available comparing different treatment approaches.

OBJECTIVE: To describe the development of knee tissue changes as observed on MRI at 2 and 5 years after ACL injury in a randomized controlled trial comparing different treatment strategies, the KANON study.

METHODS: Included were 121 subjects with an acute ACL injury in a previously uninjured knee. Repeat MRI of the index knee (baseline, 2-year and 5-year) was performed using a 1.5T system. Of the 121 participants, 117 had available MRIs at the 2-year visit and 115 at the 5-year visit. Of the subjects with available MR scans at the 2-year follow-up, 60 had received treatment with rehabilitation plus early ACL reconstruction (ACLR), 29 with rehabilitation plus delayed ACLR, and 28 with rehabilitation alone. At 5 years the number of subjects with MRIs available for the rehabilitation alone group was 26 while the other groups remained with the same number. Radiographs at baseline and at 5 years were also acquired. All available MRIs were read by one musculoskeletal radiologist according to the Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS) instrument. ACLOAS incorporates articular features relevant to a) baseline injury pattern and longitudinal follow-up of those features and b) incident degenerative features reflecting structural damage associated with OA. Intra- and inter-observer reliability was determined for 20 cases using weighted (w) kappa statistics and overall percent agreement for compartments (medial tibio-femoral joint - mTFJ, lateral tibio-femoral joint - lTFJ, patello-femoral joint - PFJ). To assess if the distribution of grades for incident degenerative BMLs, incident cartilage damage osteophytes, and inflammatory markers differed between the three 'as treated' groups (rehab only, early ACL reconstruction, delayed ACL reconstruction) $\chi^2$-tests were used. A p-value below 0.05 was considered statistically significant and all comparative analyses were performed on a knee-compartmental level.

RESULTS Patients were at baseline on average 26 years old (SD 4.9), 28 (25%) were women, and the right knee was the injured knee in 61 cases (54%). Mean body mass index was 24 (SD ± 3.2). Five years post injury, 29 (26%) patients had whole joint radiographic OA, 13 (12%) had tibiofemoral joint TFJ OA and 22 had PFJ OA (20%). At 2 (5) years, 13% (13%) knees showed any incident cartilage damage in the mTFJ, 11% (17%) in the lTFJ, and 4% (8%) knees in the PFJ. Osteophyte development was seen for 23% (29%) of knees in the mTFJ, in 36% (43%) in the lTFJ and in 35% (37%) in the PFJ. No statistically significant differences between the three 'as treated' groups were found for incident or worsening cartilage damage, BMLs and osteophytes at 2 or 5 years. The rehabilitation alone group showed less inflammation at 2 and 5 years than the surgical groups. Regarding inflammatory markers, 31% showed signs of any effusion-synovitis while 29% had grade 2 or 3 Hoffa-synovitis at year 2. At year 5, these numbers were 25% and 22%, respectively.

CONCLUSION: At 2 and 5 years after acute ACL injury, we found no statistically significant differences between treatment groups regarding frequencies of incident cartilage damage, BMLs and osteophytes. Less inflammation at 2 and 5 years in the rehabilitation alone group suggests a possible association between surgery and prolonged inflammation.

SPONSOR: The KANON study received funding for from The Swedish Research Council, the Medical Faculty of Lund University, Region Skåne, Thelma Zoegas Fund, The Stig & Ragna Gorthon Research Foundation, Swedish National Centre for Research in Sports, Crafoord Foundation, Tore Nilsson Research Fund and Pfizer Global Research.
DICLOSURE STATEMENT: Dr. Guermazi is consultant to Merck Serono, AstraZeneca, Pfizer, Roche, Galapagos, and TissuGene and is shareholder of BICL, LLC. Dr. Roemer is shareholder of BICL, LLC and consultant to Calibr - California Institute for Biomedical Research. None of the other co-authors declared potential competing interests.
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**TENDON INVOLVEMENT AND ITS ROLE IN HAND FUNCTION AND PAIN IN PATIENTS WITH OSTEOARTHRITIS OF THE HAND**

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INTRODUCTION: While tenosynovitis (TS) is a common pathological finding in rheumatoid arthritis, data on tendon involvement in hand osteoarthritis (HOA) is scarce to non-existent. The clinical examination (CE) of tendons is difficult and not fully standardized. Musculoskeletal ultrasound (US) however was shown to be a sensitive method to detect TS, tendon damage (TD) and osteophytes (OP).

OBJECTIVE: To characterize the frequency and influence of TS and TD on pain and hand function using CE and US in HOA.

METHODS: We included 86 patients with HOA. Extensor tendon compartments and flexor tendons of the hand were assessed by CE and grey scale and power Doppler US for TS, TD and OP. Global binary and semiquantitative scores were constructed. Hand function was assessed by the M-SACRAH (Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands) questionnaire and the Moberg pick-up test. Interrater reliability was assessed by Cohen's kappa, correlation with Pearson's and Spearman's rank correlation. Relationship between tendon involvement and structural damage was assessed by age- and gender-adjusted logistic binary regression.

RESULTS: Ultrasound and CE detected the involvement of ≥ 1 tendon in 60/86 patients (69.8%) and 65/85 (76.5%) patients respectively. Overall, under US, TD was detected more often in flexor tendons (0.9% vs. 2.1%, p=0.03), while TS was observed more often in extensor tendons (8% vs. 0.6%, p<0001) (Figure 1.). Only slight to no agreement was found between CE and US (TD and/or TS) on patent- and individual tendon level (kappa 0.17 and -0,009) respectively. M-SACRAH did not correlate with tendon involvement on US. Osteophytes along a tendon were associated with the occurrence of TS (OR 1.36, 95%CI 1.1-1.69; p<0.01) but not TD (OR 1.18, 95%CI 0.92- 1.51; p=0.2).

CONCLUSION: This study revealed a high frequency of tendon involvement in HOA. Osteophytes were associated with TS. Tendon involvement on US did not have an impact on hand function or pain.

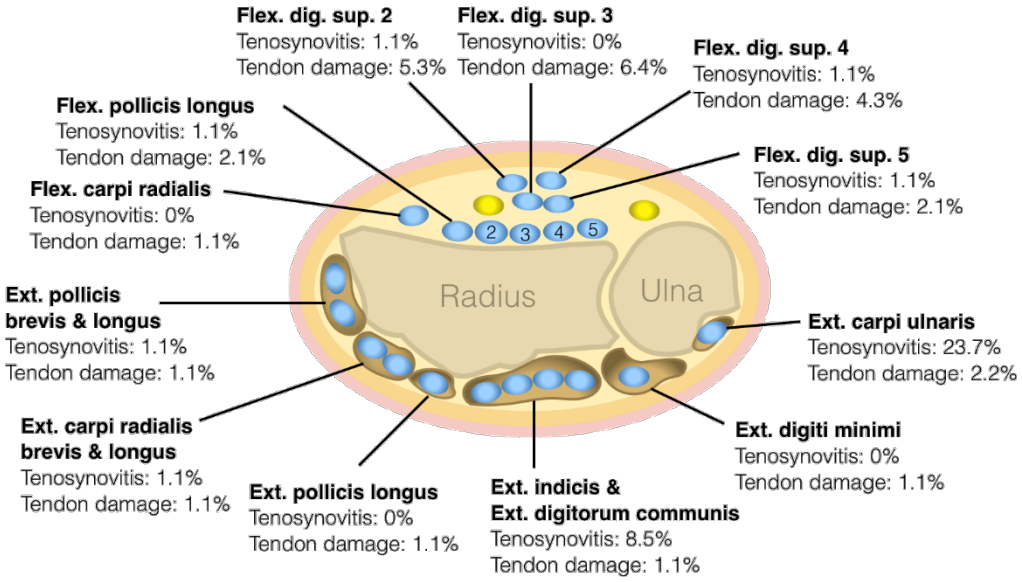


**Figure 1.** Distribution of tenosynovitis and tendon damage in the sonographic examination; Abbreviations: dig.: digitorum; ext.: extensor; flex.: flexor; sup.: superficialis. Numbers 2-5 denote respective flexor digitorum profundus tendons

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DICLOSURE STATEMENT: none
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**A DEEP LEARNING AUTOMATED SEGMENTATION ALGORITHM ACCURATELY DETECTS DIFFERENCES IN LONGITUDINAL CARTILAGE THICKNESS LOSS – DATA FROM THE FNIH BIOMARKERS STUDY OF THE OSTEOARTHRITIS INITIATIVE (OAI)**

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INTRODUCTION: Cartilage morphometry requires time-consuming expert image segmentation. Convolutional neural networks (CNNs) such as U-Nets have shown promising results for the segmentation of cartilages from MRI. However, no CNN-based method has thus far tested: 1) the sensitivity to change to longitudinal measurement, 2) the ability to differentiate rates of cartilage loss between patient groups, and 3) the impact of various training sets on the above performances.

OBJECTIVE: 1) to compare the longitudinal change and sensitivity to change observed in progressor knees from the Foundation of the National Institutes of Health (FNIH) OA Biomarkers Consortium between CNN-based automated and manual expert segmentations. 2) to study whether differences in cartilage loss between progressor and non-progressor groups can be detected by a fully automated approach. 3) to evaluate the impact of various (combinations of) training sets on these measurements.

METHODS: FNIH progressor knees had both medial tibiofemoral radiographic joint space width loss (≥0.7 mm) and a persistent increase in WOMAC pain (≥9 on a 0-100 scale) after 2 years from baseline (n=194), whereas non-progressor knees did not (n=200). CNN-based U-Nets were trained on knees with radiographic OA (ROA) not part of the FNIH study (n=86/18 training/validation set), both baseline and 2-year follow-up MRIs of these ROA knees (ROA BL+FU), OAI healthy reference cohort (HRC) knees (n=50/21 training/validation), and both the ROA and HRC knees (ROA+HRC). These models were then used to automatically segment medial (MFTC) and lateral femorotibial cartilage over two-years. Findings were compared with previously published manual expert segmentation.

RESULTS: The MFTC cartilage loss in the full progressor subcohort was -181±245µm by manual (SRM=-0.74), -144±200µm by ROA U-Net (SRM=-0.72), -127±203µm by ROA BL+FU U-Net (SRM=-0.63), -69±231µm by HRC U-Net (SRM=-0.30), and -116±284µm by ROA+HRC U-Net segmentation (SRM=-0.41). Cohen's D between full vs. non-progressor knees was -0.84 ($p<0.001$) for manual, -0.68 ($p<0.001$) for ROA U-Net, -0.60 ($p<0.001$) for ROA BL+FU U-Net -0.14 ($p=0.18$) for HRC U-Net, and -0.40 ($p<0.001$) for ROA+HRC U-Net segmentation.

CONCLUSION: Fully automated U-Net-based cartilage segmentation trained on ROA knees displayed similar sensitivity to change of longitudinal cartilage thickness loss in knee OA as manual expert segmentation. Further, it effectively differentiated longitudinal rates of cartilage thickness loss between progressor and non-progressor knees. U-Nets trained on HRC knees only, or a combination of ROA and HRC knees showed inferior performance. Training on both baseline and follow-up segmentations from ROA knees did not improve the sensitivity to change or detection of between-group differences.

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**3D CONTOUR REGISTRATION REVEALS THAT LOCATION-INDEPENDENT CARTILAGE THICKNESS SCORES AND REGIONAL PATTERNS DIFFER BETWEEN EARLY AND LATE FOLLOW-UP AFTER ANTERIOR CRUCIATE LIGAMENT (ACL) RUFTURE**

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INTRODUCTION: ACL rupture is associated with acute joint trauma and chronically altered joint mechanics as well as an increased risk of incident knee OA. It has been previously reported that femorotibial cartilage thickness increases significantly in young adults after ACL rupture, and at a similar rate during the first 2 years (BL→Y2) and the subsequent 3 years (Y2→Y5).

OBJECTIVE: To compare annualized location-independent cartilage thickness change scores, and regional patterns, obtained from 3D contour registration, in knees of young active adults with acute ACL rupture during early (BL→Y2) vs. later (Y2→Y5) follow-up (FU).

METHODS: Sagittal DESS MRIs from 121 acutely ACL ruptured knees from a published RCT with manual femorotibial cartilage segmentations were used. To compare thickness changes for each voxel (0.29 x 0.29 x 1.5 $mm^3$), BL and FU images were unimodally registered based on segmented subchondral bone (tAB) contours of the femorotibial cartilages. Thickness values, and BL→FU differences, were computed for each tAB voxel for MT, cMF, LT, an cLF. The summed positive changes (thickening score), the negative ones (thinning score), and total changes independent of direction (change score) were annualized and statistically compared (paired t-test, Cohen D [CD]) between both observation periods.

RESULTS: In all 4 cartilage plates, the annualized location-independent cartilage thickness change scores were statistically significantly ($p<0.001$) greater during BL→Y2 than during Y2→Y5. Effect sizes (CD) were 1.6 for MT, and 1.2 for cMF, LT and cLF, respectively. The same applied to the thickening and thinning scores, with regional patterns for BL→Y2 shown in Fig. 1. During BL→Y2 Thickening/ thinning ratios were observed to be 1.13 for MT, 1.20 for cMF, 1.14 for cLF, but only 0.73 for LT.

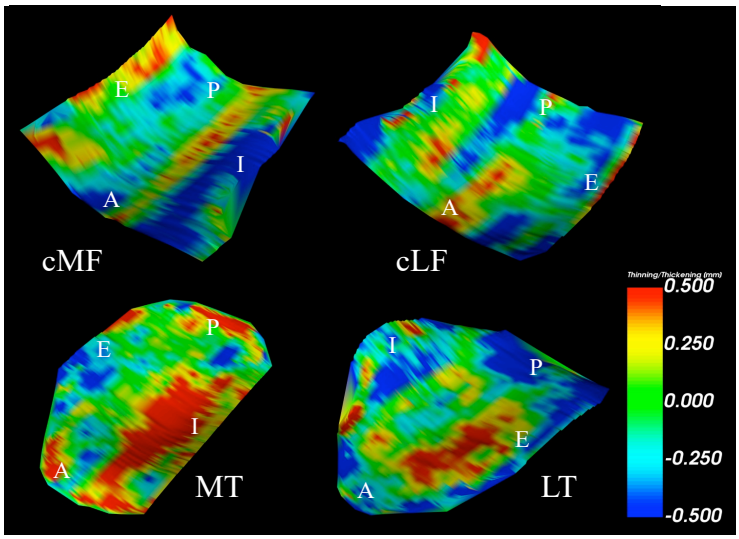


**Fig. 1:** Regional patterns of cartilage thickness change (left knee) (A=anterior; P=posterior; I=Internal; E=External)

CONCLUSION: This is the first study to use 3D contour registration for obtaining location-independent cartilage thickness change scores for each femorotibial cartilage plate, exploiting high-resolution (voxel-based) information. Both cartilage thinning and thickening were greater during early than during later FU, an observation that remains hidden, when only overall cartilage volume or thickness change are measured. Most thinning was observed for LT, the site of greatest mechanical impact during ACL tear.

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**AUTOMATED MEASUREMENT OF LOCAL, MRI-BASED MEASURES OF THIGH ADIPOSE AND MUSCLE TISSUE ARE HIGHLY RESPONSIVE TO BIDIRECTIONAL CHANGE IN BODY WEIGHT - DATA FROM THE OSTEOARTHRITIS INITIATIVE**

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INTRODUCTION: Thigh intermuscular (IMF) and subcutaneous (SCF) fat tissue, and muscle composition are associated with knee function. The responsiveness of IMF and SCF, and muscle, to bidirectional change in weight has not been systematically studied, and the performance of an automated segmentation algorithm has not been clinically validated in this context.

OBJECTIVE: 1) to explore the responsiveness of IMF and SCF during weight loss and gain, 2) to compare the performance of an automated algorithm vs. manual segmentation, 3) to compare the responsiveness of these adipose tissue measures between men and women, 3) to explore whether muscle anatomical cross-sectional areas (ACSAs) are responsive to weight loss/gain.

METHODS: All 4,796 Osteoarthritis Initiative (OAI) participants who displayed a >10% weight loss/gain between baseline and 2-year (Y2) follow-up, and who maintained ≥5% of that weight change at Y4 follow-up were studied. Axial 3T T1w SE MRIs were used to analyze thigh tissue composition at a consistent anatomical location (33% femoral length from distal to proximal). Longitudinal change in IMF, SCF, extensor and flexor muscle (m.) ACSAs were determined from baseline and Y2 MRIs, using manual segmentation, as well as a published fully automated algorithm using a U-net deep learning architecture. Within-subject changes (baseline →Y2) were tested for statistical significance using paired t-tests. The SRM was used as a measure of sensitivity to change.

RESULTS: 52 OAI participants had >10% weight loss and 51 displayed a >10% weight gain. IMF and SCF both showed a significant decrease with weight loss and increase with weight gain in both men and women; the automated measurements (Table 1) were highly consistent with manual ones (data not shown). The magnitude of the changes was similar for loss and gain, and similar in men and women (Table 1). Men and women with weight loss encountered substantial reductions in muscle ACSAs, but much smaller changes in muscle ACSAs were observed with weight gain (Table 1).

| **Table 1** | **Weight Loss** | | **(* p<0.05)** | | | **(* p<0.05)** |
|---|---|---|---|---|---|---|
| | **Men** | | | **Women** | | |
| | **Diff %** | **95%CI** | **SRM** | **Diff %** | **95%CI** | **SRM** |
| IMF (%) | -14 % | (-20, -8) | -1.30* | -14 % | (-19, -10) | -0.82* |
| SCF (%) | -21 % | (-33, -9) | -1.04* | -24 % | (-29, 19) | -1.25* |
| Ext. m. (%) | -6.4 % | (-9.8, -3.0) | -1.08* | -9.0 % | (-11, -6.8) | -1.23* |
| Flexor m. (%) | -9.2 % | (-16, -2.8) | -0.83* | -6.6 % | (-8.9, -4.3) | -0.94* |
| | **Weight Gain** | | **(* p<0.05)** | | | **(* p<0.05)** |
| IMF (%) | +16 % | (10, 21) | 1.38* | +10 % | (6.0, 14) | 0.83* |
| SCF (%) | +30 % | (18, 42) | 1.31* | +25 % | (15, 34) | 0.92* |
| Ext. m. (%) | +1.7 % | (-0.8, 4,2) | 0.35 | +0.8 % | (-1.8, 2.0) | 0.01 |
| Flexor m. (%) | +1.9 % | (-1.0, 4,9) | 0.33 | +4.0 | (2.1, 5.9) | 0.75* |

CONCLUSION: Automated MRI measures of thigh adipose (IMF and SCF) and muscle tissue were found to be highly responsive to bidirectional change in body weight, both in men and women and to provide similar results to manual segmentation. The overall findings highlight that MRI represents a sensitive tool for exploring how thigh adipose and muscle tissue composition may respond to different conditions of weight loss or gain in both sexes, for instance during specific diet and/or exercise interventions, or under microgravity conditions.

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**ARTIFICIAL INTELLIGENCE-BASED AUTOMATED ANALYSIS OF ALIGNMENT IN FULL-LEG RADIOGRAPHS**

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INTRODUCTION: The gold standard for assessment of malalignment as a biomechanically contributing factor to knee OA is the weight-bearing long-leg radiograph (LLR). Manual measurements of relevant axes and angles may be prone to subjectivity and are time-consuming and cognitively simple for radiologists. Hence, in this era of much-sought standardization of image analysis, we have developed an artificial intelligence-based support system for automatic post-processing and analysis of LLRs without any additional user input.

OBJECTIVE: The aim of this study was to evaluate the performance of a fully-automated analysis algorithm for LLRs that automatically segments femoral and tibial bone contours, identifies anatomical landmarks, and determines relevant mechanical and anatomical axes as compared to manual reference measurements performed by two radiologists.

METHODS: From our clinical routine, we included bilateral weight-bearing LLRs of 271 consecutive patients that were split into training set (n=120), validation set (n=41), and testing set (n=110). Following manual reference segmentations of the bone contours of femur and tibia in the training and validation sets (Fig. 1a), automated segmentation algorithms using a U-Net-based Convolutional Neural Network architecture were optimized. Linear least-squares-fitting techniques were used to determine the anatomical axes, while iterative algorithms were used to identify anatomical landmarks, i.e. center of the femoral head, apex of the femoral notch, femoral and tibial joint levels, and center of tibial plafond. Based on these landmarks, anatomic and mechanical axes were automatically determined (Fig. 1b) and quantified as the anatomic-mechanical angle (AMA; Fig 1c) and the hip-knee-ankle angle (HKA; Fig. 1d). Manual reference measurements were performed by two radiologists-in-training (MP, FM) using the digital toolbox of the in-house PACS (Philips). Pearson's correlation determined to quantify inter-rater agreement, i.e. between radiologist 1, radiologist 2, and the automated algorithm-based approach.

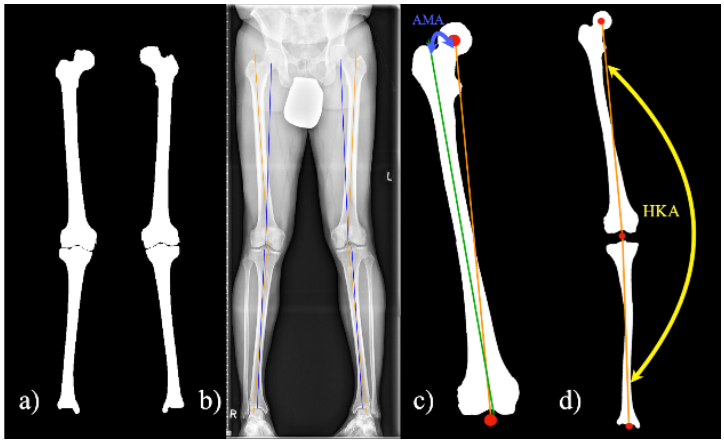


**Figure 1:** Following automated segmentation of the bilateral femoral and tibial bone contours (a), the anatomic (orange) and mechanical (blue) femoral and tibial axes were automatically determined and overlaid onto the corresponding radiograph (b). Alignment of the lower extremity was quantified in terms of the anatomic-mechanical angle (AMA, c), defined as the angle between the mechanical and anatomical femoral axes, and the hip-knee-ankle angle (HKA, d), defined as the angle between the femoral and tibial mechanical axes.

RESULTS: After ongoing optimizations, automatic segmentations achieved very high correspondence with manual segmentations (validation dataset, Sørensen-Dice coefficient 0.994). Similarly, for both HKA and AMA, high Pearson's correlation coefficients were determined between the manual and algorithm-based measurements (HKA: $0.89 \leq r \leq 0.90$; AMA: $0.98 \leq r \leq 0.99$), indicating excellent agreement.

CONCLUSION: Using artificial intelligence-based image processing techniques, fully automated quantitative analysis of lull-leg radiographs allows standardized and reproducible determination of clinically relevant measures of alignment that are highly concordant with radiologists' manual definitions and may streamline image post-processing in clinical studies.

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**FREQUENCY OF OSTEOARTHRITIS IN ATHLETES UNDERGOING MRI AT THE OLYMPICS IN RIO 2016**

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INTRODUCTION: In high-level athletes, injuries and repetitive trauma are common and thought to be risk factors for OA development. There is no data available regarding frequencies of structural OA in active Olympic athletes.

OBJECTIVE: To describe the frequency and severity of osteoarthritis (OA) in athletes participating in the Rio de Janeiro 2016 Summer Olympic Games as assessed using magnetic resonance imaging (MRI).

METHODS: The current study is based on a retrospective analysis of all MRIs of athletes who underwent MRI at the centralized core imaging facility of the International Olympic Commission (IOC) during the Rio 2016 Summer Olympics. Athletes were imaged for a multitude of reasons but had MRI mainly for suspected structural damage following acute trauma or non-traumatic pain. MRI imaging was performed within the Olympic Village through the official IOC clinic, using 3T Discovery MR750w and 1.5T Optima 450 MRw MR systems (both GE Healthcare, Brazil). All MRIs were reviewed for presence and severity of OA features primarily by one radiologist adjudicated by a second experienced radiologist. Scoring of MRI abnormalities was blinded to the initial reports. The MRIs of six anatomical regions / articulations were included and assessed retrospectively: shoulders, elbows, wrists, hips, knees and ankles. Osteophytes were scored as present (=definite osteophyte) or absent, and cartilage damage was scored from 0 to 3 according to a modified Outerbridge scale. These data were grouped into different severity grades. Proportion of OA was tabulated for the entire sample, and grouped into sports categories (athletics, ball sports, other). In addition, results were categorized according to age strata (<25; 25-30; and >30 years of age) and by sex.

RESULTS: A total of 11,274 athletes participated in the Games. 319 (2.8%) athletes underwent MRI of one or more of the mentioned anatomic locations. 160 (50.2%) were female, 109 (34.2%) were < 25 years, 131 (41.1%) between 25 and 30, and 79 (24.8%) > 30 years of age. 53 (16.6%) of the athletes that had MRI examinations were found to have underlying OA with 13 (4.1%) having mild OA, 13 (4.1%) moderate, and 27 (8.5%) severe OA. Within the category of ball sports knees were found to have the highest prevalence of OA with 9.6%. Within the categories of athletics and other sports, wrists were found to have the highest prevalence of OA at 4.2% and 21.0%, respectively. Of all athletes younger than 25 years 11 (10.1%), of those between 25-30 years of age 24 (18.3%) and of those older 30 years of age 18 (22.8%) were found to have OA. Of all athletes with OA the wrist (29.2%) and the knee (23.3%) were most commonly affected. (Table 1).

**Table 1.** Frequency and severity of OA in the athletes who participated in Rio Olympics in 2016

| | No OA (%) | Any OA (%) | Mild OA (%) | Moderate OA (%) | Severe OA (%) | Ball sports, OA (%) | Athletic sports, OA (%) | Other sports, OA (%) |
|---|---|---|---|---|---|---|---|---|
| Knee | 95 (76.6) | 29 (23.4) | 0 | 8 (6.5) | 21 (16.9) | 12 (9.6) | 5 (4.0) | 12 (9.6) |
| Hip | 39 (97.5) | 1 (2.5) | 1 (2.5) | 0 | 0 | 0 | 1 (2.5) | 0 |
| Shoulder | 48 (87.3) | 7 (12.7) | 0 | 2 (3.6) | 5 (9.1) | 2 (3.6) | 2 (3.6) | 3 (5.4) |
| Elbow | 12 (85.7) | 2 (14.2) | 0 | 1 (7.1) | 1 (7.1) | 1 (7.1) | 0 | 1 (7.1) |
| Ankle | 82 (89.1) | 10 (10.9) | 10 (10.9) | 0 | 0 | 2 (2.2) | 1 (1.1) | 7 (7.6) |
| Wrist | 17 (70.8) | 7 (29.2) | 4 (16.7) | 2 (8.3) | 1 (4.2) | 1 (4.2) | 1 (4.2) | 5 (21.0) |
| <25 years old | 98 (89.9) | 11 (10.1) | 3 (2.8) | 2 (1.8) | 6 (5.5) | | | |
| 25-30 years old | 107 (81.7) | 24 (18.3) | 5 (3.8) | 6 (4.6) | 13 (9.9) | | | |
| >30 years old | 61 (77.2) | 18 (22.8) | 5 (6.3) | 5 (6.3) | 8 (10.1) | | | |
| All sports | 266 (83.4) | 53 (16.6) | 13 (4.1) | 13 (4.1) | 27 (8.5) | 18 (32.1) | 10 (17.9) | 28 (50.0) |

CONCLUSION: In this highly selected sample of athletes that underwent MRI of one of 6 major joints at the Rio Summer Olympics a frequency of 16.6% of any osteoarthritis on MRI was observed. Severe OA was more common than low or moderate OA possibly reflecting that these athletes are more likely to receive an MRI during competition than others. Of athletes with OA, the wrist was the most likely anatomic location to be involved. Frequency of OA was higher in athletes of 30 years or older.

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DICLOSURE STATEMENT: Ali Guermazi is consultant to Merck Serono, AstraZeneca, Pfizer, Roche, Galapagos, and TissuGene and is shareholder of BICL, LLC. Dr. Roemer is shareholder of BICL, LLC. Frank Roemer is consultant to Calibr - California Institute for Biomedical Research. None of the other co-authors declared potential competing interests.
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**BIOMECHANICAL IMAGING OF PROTEOGLYCAN-DEPLETED HUMAN ARTICULAR CARTILAGE – A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY**

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INTRODUCTION: The functional properties of human articular cartilage are determined by the complex interplay of its principal fluid and solid constituents, i.e. interstitial water, collagen, and proteoglycans. If the interplay is altered, the tissue's susceptibility to premature degeneration and osteoarthritis is increased.

OBJECTIVE: The aim of this study was to define the dose-dependent effects of trypsin-induced proteoglycan depletion on human articular cartilage functionality as assessed by serial quantitative Magnetic Resonance Imaging (qMRI) under simultaneous loading. Our hypotheses were that trypsin exposure alters cartilage composition and cartilage functionality as a function of concentration and that loading-induced changes in T1, T1ρ, T2, and T2* were reflective of these alterations.

METHODS: Macroscopically intact osteochondral samples were obtained from the lateral femoral condyles of total joint replacement surgeries (n=29) and prepared to standard size and configuration. Samples were subject to serial morphological and functional imaging by Proton Density-weighted and T1 (inversion recovery), T1ρ (spin-lock multigradient echo), T2 (multi-spin echo), and T2* (multi-gradient echo) mapping sequences on a clinical 3.0 T MRI scanner (Achieva, Philips). By means of a pressure-controlled indentation loading device (Fig. 1a), samples were serially imaged, i.e. unloaded ($\delta_0$) and quasi-statically loaded to 15.1 N ($\delta_1$) and to 28.6 N ($\delta_2$), both before and after exposure to low-concentrated trypsin (LT, 0.1 mg/mL, n=10) or high-concentrated trypsin (HT, 1.0 mg/mL, n=10) (Fig. 1b-e). Control samples were not treated (n=9). Following manual segmentation, the response to loading was assessed both regionally and zonally as well as for the entire sample. Regions were defined in relation to the loading piston as sub-pistonal (directly loaded) and peri-pistonal (adjacent) tissue areas, while zones were defined as the upper and the lower sample halves. Trypsin effects were quantified as relative changes in the respective qMRI parameter (Δx) and analysed using appropriate statistical tests. Histology served as reference (Fig. 1f).

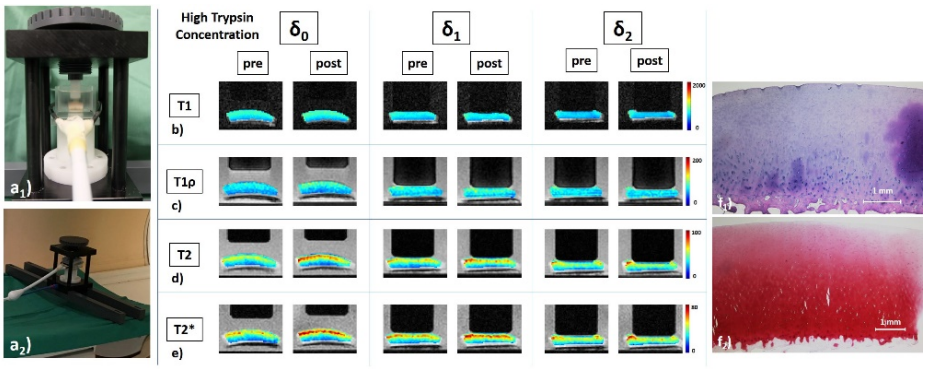


**Figure 1:** Details of experimental setup (a), images of an exemplary high-concentration trypsin-treated cartilage sample and its response to loading (b-e), and corresponding histological sections (f). An MRI-compatible pressure-controlled indentation loading device was used to load cartilage in a standardized manner. Serial quantitative T1 (b), T1ρ (c), T2 (d), and T2* (e) maps as well as corresponding histological sections (f, HE staining [$f_1$], Safranin O staining [$f_2$]) of a representative cartilage sample before and after exposure to high concentration of trypsin at 1.0 mg/mL

RESULTS: Dose-dependently, proteoglycan depletion was observed to involve superficial and transitional tissue zones, which was reflected by significant sub-pistonal decreases in T1 ($p=0.003$, $\Delta_2$) and T2 ($p=0.008$, $\Delta_2$) after HT exposure. Loading-induced changes in T1ρ and T2* were not clearly related to loading intensity or trypsin exposure.

CONCLUSION: Proteoglycan depletion -one of the earliest changes of cartilage degeneration- alters tissue functionality and may be best assessed using serial T1 and T2 mapping under loading.

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**EFFECTS OF SPORTS CLIMBING ON CARTILAGE STRUCTURAL COMPOSITION OF THE METACARPO-PHALANGEAL AND PROXIMAL INTERPHALANGEAL JOINTS AS ASSESSED BY T2 RELAXOMETRY AT 7T MRI**

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INTRODUCTION: Different sport activities expose athletes to unique patterns of musculoskeletal adaptations and joint injuries. Climbing sport strains finger joints to high loads during repetitive tension and compression motion. However, there is paucity of data regarding the influence of climbing sport on finger joint cartilage of young athletes compared to healthy controls. 7.0 Tesla (T) MRI has the highest magnetic field strength approved for routine clinical image acquisition and high magnetic field strength may contribute to improved spatial resolution, higher signal intensity and higher signal to noise ratios (SNR), enabling cartilage imaging also of finger joints.

OBJECTIVE: To evaluate whether climbing activity and age is associated with differences in cartilage composition based on T2 relaxometry of the metacarpophalangeal and proximal interphalangeal joints compared to non-climbing controls at 7T MRI.

METHODS: Included were 13 long-time climbers without history of trauma who were regularly performing climbing activities as a recreational sport (>10 hours/month) on an advanced level. All individuals had performed climbing sport for at least 5 years (mean 7.8 ± 3.2 years). The subjects were age-matched with 10 healthy control subjects not performing climbing sport. 7T MRI (Siemens Magnetom TERRA) of the second, third and fourth finger was performed with a dedicated wrist coil using a multi-echo spin echo sequence. The Time of Repetition (TR) was 3050 ms with Echo Times (TE) of 17.1, 34.2, 51.3, 68.4, 85.5 and 102.6 ms. The pixel size was 0.2 x 0.2 mm, the slice thickness 2.5 mm. Manual segmentation was performed for five regions of interest (ROI) (Figure 1). T2 relaxation times were created using a pixel-wise, mono-exponential, non-negative least squares (NNLS) fit analysis (MapIt, Siemens Medical Solutions, Erlangen, Germany). A mixed error-component model was applied considering ROI, finger, age and climbing activity as predictors and T2 values as the outcome.

RESULTS Mean age was 32 years for the climbing group and 26 years for the controls. Mean T2 values for the 5 different ROIs (ROI 1: 32.5 ± 10.8; ROI 2: 45.2 ± 12.4; ROI 3: 36.2 ± 8.2; ROI 4: 49.8 ± 12.0; ROI 5: 39.9 ± 11.6) were 40.7 ± 10.9 msec for climbers and 39.1 ± 11.2 msec for non-climbers (ROI 1: 29.6 ± 10.6; ROI 2: 46.4 ± 13.7; ROI 3: 33.7 ± 8.3; ROI 4: 50.6 ± 12.1; ROI 5 35.3 ± 11.6). No significant differences were observed for T2 values between both groups. Contrary to that, higher age had a significant impact on T2 values for all assessed ROIs (44.2 ± 9.5 vs. 32.9 ± 5.7, p = 0.001) (Figure2), whereas sex did not show any influence on T2 values.

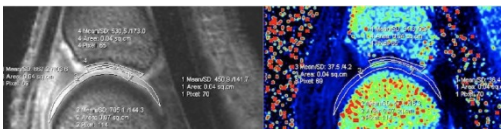

**Figure 1**. Manual segmentation. Left side of figure shows segmentation of the five ROIs, i.e. three at the metacarpal heads (anterior (1), central (2), posterior (3), one at the base phalanx (4) and one at the proximal interphalangeal joint (5). Right side of image shows color-coded T2 map.

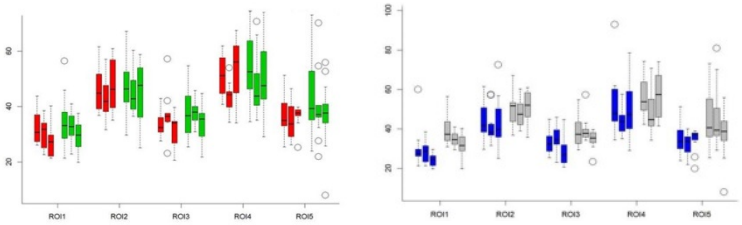


**Figure 2**. Influence of climbing and age on cartilage T2. ROIs 1 to 4 represent the MCP joints and ROI 5 the PIP joint of D2-4. Left graph shows the comparison between climbers (red bars) vs. non climbers (green bars). Right bar graph compares subjects older (gray bars) vs. younger (blue bars) 27 years of age.

CONCLUSION: Climbing activity in subjects without prior trauma did not seem to have an impact on cartilage composition of metacarpal-phalangeal and proximal interphalangeal joints. However, older subjects consistently exhibited higher T2 values compared to younger subjects. Age-related effects seem to be more prominent in regard to cartilage composition compared to influence of climbing activity. Our study does not suggest that climbing activity has a negative impact on cartilage composition in young, active climbers as assessed at 7T MRI.

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# POSTERS

**DISTRIBUTION OF MEDIAL FEMUR AND TIBIA CARTILAGE CHANGE ON MRI: COMPARISON BETWEEN KL GRADES**

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INTRODUCTION: Semi-automated Local Area Cartilage Segmentation (LACS) software uses robust coordinate systems to measure cartilage change in focused regions in the femur and tibia. LACS also offers a topological method to assess cartilage volume change through the use of responsiveness heat maps.

OBJECTIVE: Provide a descriptive assessment of the distribution of cartilage change in sub-regions of the MF and MT for different KLG.

METHODS: The cartilage volume was measured in a central weight-bearing portion of the MF and MT using the LACS method at the baseline (BL) and 48-month visits of 121 OAI participants. Cartilage change was calculated as standardized response mean (SRM) for both plates separately. Finally, LACS SRM was estimated over grids in the sample and displayed in the form of responsiveness heat-maps, showing topographical change of each cartilage plate. The mathematical nature of the LACS method permits any grid location to be determined consistently.

RESULTS: The participants had a mean age of 60.6 years at BL, were 61.1% female, and the BL KLG were distributed as follows: KL1: N=34, KL2: N=59, KL3: N= 28. SRM values are given in Table 1. The responsiveness heat-maps are shown in Figures 1 and 2. We observe an increase in responsiveness with higher KLG and observe different patterns of change in heat-maps.

| | KL1 (N=34) | KL2 (N=59) | KL3 (N=28) | All (N=121) |
|---|---|---|---|---|
| MF | -0.54 | -0.52 | -0.91 | -0.61 |
| MT | -0.46 | -0.72 | -0.73 | -0.66 |

**Table 1.** SRM values for different KL grades

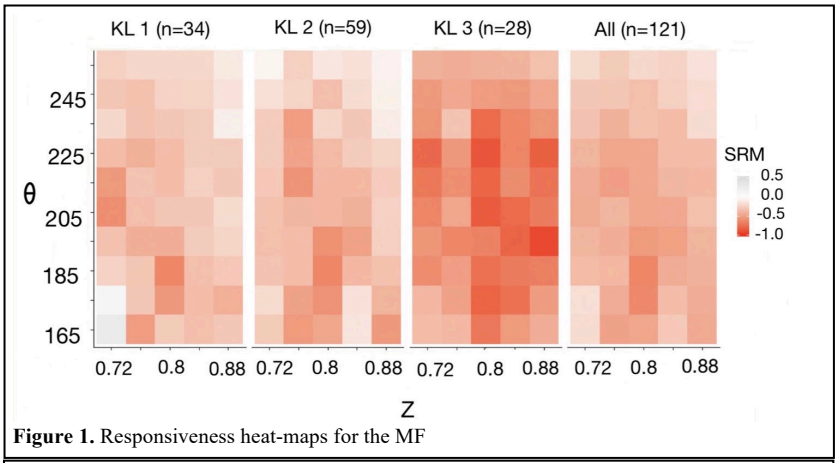


**Figure 1.** Responsiveness heat-maps for the MF

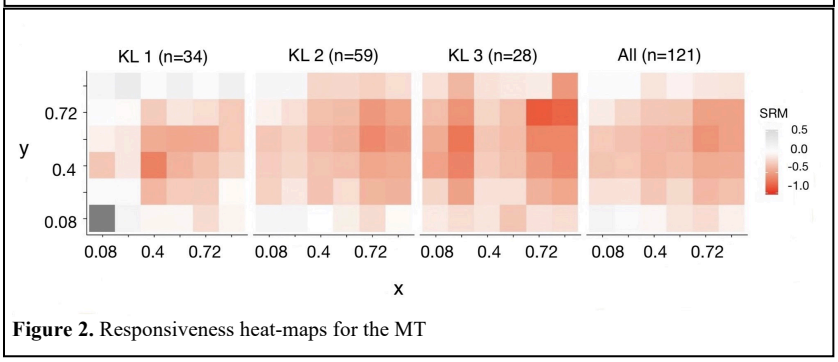


**Figure 2.** Responsiveness heat-maps for the MT

CONCLUSION: The different patterns of change by KLG suggest that the heat-map approach may offer a way to characterize different disease-related patterns of KOA progression. Additional study will be necessary to better understand the role of responsiveness heat-maps in studies of KOA.

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DISCLOSURE STATEMENT: RA, HR, AM, JD: None. CKK, ELA: Consultants for EMD Serono. CKK: Grant/research support from EMD Serono, Thuasne, Express Scripts, Regeneron, LG Chem, Kolon Tissue Gene. Grants: Abbvie, Lilly, Pfizer, GSK.
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**EVALUATING DEEP LEARNING 2D ARCHITECTURES IN OAI CHALLENGE**

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INTRODUCTION: The assessment of a drug's efficacy in joint OA treatment critically relies on the quantitative monitoring of the disease progression through metrics such as cartilage thickness. With MRI offering more accurate and comprehensive data than previous techniques on cartilage in the knee [1], efforts to drive down its prohibitive costs have risen in popularity. Our work targets the process of segmenting cartilage, which entails lengthy expert labelling of cartilage tissues in scan volumes and presents a cost hurdle to treatment trials. While atlas-based approaches currently attempt to automate segmentation in medical imaging, their rigidity and inability to generalize leaves room for improvement. Recent developments in deep learning for medical imaging, such as the U-Net architecture, show promise in addressing such issues and have so far achieved remarkable accuracy in knee MRI scans. Such algorithms could speed up the work of radiologists and ultimately lower the cost associated with MRI processing.

OBJECTIVE: We expand on previous work in deep learning for medical image segmentation [2] by comparing the accuracy achieved by several model architectures, as well as testing the hypotheses that:
1) multi-class segmentation of cartilages achieves results comparable to binary segmentation of cartilages
2) the increasingly complex models we train perform better than the previously tested vanilla U-Net

METHODS: The dataset at our disposition consists of 148 volumes acquired from the OAI challenge initiative, where each volume is a 3T MR scan with dimensions (384, 384, 160). We crop the volumes to (288, 288, 160) to remove redundant background regions and reduce artifacts, upon which we utilize geometric transformations to augment the data sample. To account for the computational burden of training on 3-dimensional data, we feed our segmentation model with MRI scans in a slice by slice manner. With the intention of improving on results obtained in [2], we simultaneously train on the baseline U-Net architecture [3] used in [2] and on several deeper segmentation architectures, i.e. U-Net-based models, DeepLabv3 [4], 100-Layer Tiramisu [5] by differentiating the predicted cartilage in both binary and multi class fashions. A comparative analysis across these is enabled by evaluating the results on a common set of metrics as well as employing custom visualization tools in order to carry out a qualitative comparison between predicted and expected outputs.

RESULTS: In binary segmentation setting, the 100-Layer Tiramisu achieved the best dice coefficient at 0.9102. On the other hand, the baseline U-Net model performs the best in multi-class segmentation with a mean dice coefficient of 0.8605 across the cartilage classes. Comparison of model performance between binary and multi-class segmentation highlights the difficulty of complex models to converge in multi class segmentation and the need for a larger training dataset to prevent overfitting.

CONCLUSION: Our experimental results show that on the OAI challenge dataset, increasing model complexity does not guarantee improved segmentation accuracy, especially in multi-class segmentation setting. However, we believe that with larger training dataset and extensive hyperparameter search, we expect more complex model architectures to converge to their global optimum and potentially outperform the baseline U-Net model.

DICLOSURE STATEMENT: Our supervisor previously published with A. Chaudhari.
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**BASELINE CHARACTERISTICS OF THE STUDY POPULATION IN ROCCELLA, A PHASE 2 CLINICAL TRIAL EVALUATING THE EFFICACY AND SAFETY OF S201086/GLPG1972 IN PATIENTS WITH KNEE OSTEOARTHRITIS**

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INTRODUCTION: Degradation of the cartilage extracellular matrix represents a central feature of osteoarthritis (OA) and is widely thought to be mediated by proteinases that degrade primarily aggrecan and collagen. ADAMTS-5, a Disintegrin And Metalloproteinase with ThromboSpondin-motif-5, is a key aggrecan-cleaving enzyme involved in cartilage degradation. S201086/GLPG1972, a potent and highly selective inhibitor of ADAMTS-5, is an oral Disease-Modifying OsteoArthritis Drug (DMOAD) candidate.

OBJECTIVE: The primary objective of the ROCCELLA phase 2 clinical trial (NCT03595618) is to evaluate the effect of S201086/GLPG1972 on cartilage loss in the knee, over 52 weeks of treatment. Here, we describe the baseline characteristics of patients included in the ROCCELLA clinical trial.

METHODS: Eligible participants were aged 40–75 years, with a diagnosis of knee OA according to the clinical and radiological criteria of the American College of Rheumatology and a pain score of 40–90 mm on a 100 mm Visual Analog Scale (VAS). Target knees had a Kellgren/Lawrence (KL) grade of 2 or 3 and OARSI medial joint space narrowing (JSN) grade of 1 or 2 (for more details see Deckx *et al*. IWOAI 2020). These specific radiographic inclusion criteria were chosen to ensure sufficient cartilage loss in the placebo group over 12 months to assess the efficacy of S201086/GLPG1972.

RESULTS: Of 3319 patients screened across 12 countries, 932 were included. Most participants were female (69.3%) and the mean age was 62.9 years (standard deviation [SD], 7.3). Participants had a mean BMI of 30.5 $kg/m^2$ (SD, 4.7) and the mean duration of knee OA was 7.2 years (SD, 6.9). Overall, 501 participants (53.8%) reported a medical history of musculoskeletal and connective tissue disorders, mainly OA in other sites (20.2%), back pain (13.6%), and arthralgia (9.8%). At inclusion, 97.2% of participants were taking different types of drug treatments, mainly anti-inflammatory and anti-rheumatic products (69.4%) and analgesics (42%). At baseline, 11% of target knees had a KL grade of 2 and 89% had a KL grade of 3; 32% were OARSI medial JSN grade 1 and 68% grade 2. The mean baseline VAS score was 63.5 mm (SD, 11.4) and the mean total WOMAC (Likert 3.1) score was 48.0 (SD, 15.0; range 0–96). WOMAC subscores for pain, stiffness and physical function were 10.0 (SD, 3.2; range 0–20), 4.2 (SD, 1.6; range 0–8) and 33.8 (SD, 11.2; range 0–68, indicating functional limitation), respectively.

CONCLUSION: For this clinical trial, patients were selected to present radiological criteria to ensure sufficient structural progression (cartilage loss) over 12 months, as well as clinical symptoms. These stringent selection criteria were the main cause for the high screen failure rate. These baseline characteristics should warrant the ability to evaluate the structural therapeutic efficacy of S201086/GLPG1972 as a DMOAD candidate. The search for an effective pharmacological treatment that can prevent, or cure OA remains a major challenge and represents an unmet medical need.

SPONSOR This study was funded by the Institut de Recherches Internationales Servier (Suresnes, France) and Galapagos NV (Mechelen, Belgium).
DISCLOSURE STATEMENT: K. Bernard, S. Grankov, A. Lalande, O. Imbert, D. Chimits and M. Pueyo are employees of Institut de Recherches Internationales Servier. M. van der Stoep, D. Phung, K. Muller, E. van der Aar and H. Deckx are employees of Galapagos NV. F. Eckstein is co-owner and employee of Chondrometrics and has received consulting fees from: Merck, Bioclinica, Servier, Samumed, Roche, Kolon Tissuegene, Galapagos and Novartis
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**THE HEALING OF CONSERVATIVELY-TREATED SCAPHOID FRACTURES ASSESSED BY HIGH-RESOLUTION PERIPHERAL QUANTITATIVE COMPUTED TOMOGRAPHY**

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INTRODUCTION: The healing of a scaphoid fracture can be challenging. Adequate monitoring of fracture healing may improve clinical outcome but is limited with currently used imaging modalities.

OBJECTIVE: The aim of this study was to assess the healing of conservatively-treated scaphoid fractures at microarchitectural level with high-resolution peripheral quantitative computed tomography (HR-pQCT).

METHODS: HR-pQCT scans were acquired of the scaphoid bone of fourteen patients with a scaphoid fracture confirmed on HR-pQCT and treated with a cast. The scans were taken at baseline - within 10 days after initial presentation at the emergency department (ED) - and at three, six, twelve, and 26 weeks after initial presentation. They were analyzed to quantify bone mineral density, microarchitecture, and ultimate force. Linear mixed-effects models were used to evaluate longitudinal changes in the parameters.

RESULTS: Data of three patients were excluded due to absence of a scaphoid fracture and change to surgical treatment. In the remaining eleven patients, median time to cast removal was 6.6 (IQR: 4.3) weeks. In these patients, the fracture line was more apparent at three weeks after initial presentation than at baseline, and there was blurring of the fracture region at six and twelve weeks after initial presentation (see Fig.1). Small surface and trabecular disruptions were visible in some fractures at 26 weeks. Density, trabecular thickness, and ultimate force significantly decreased compared to baseline and showed a minimum at six weeks after initial presentation (-13.6%, -6.7%, and -23.7% compared to baseline, respectively). Thereafter, density stabilized and ultimate force increased and both remained significantly lower than baseline at twelve and 26 weeks after initial presentation. Trabecular thickness also increased after six weeks and remained significantly lower than baseline at twelve weeks. Trabecular number decreased to a minimum at 26 weeks (-7.9% compared to baseline) and was significantly lower than baseline at six, twelve, and 26 weeks. Trabecular separation was significantly higher than baseline at the same timepoints with a maximum at twelve weeks (+19.7% compared to baseline).

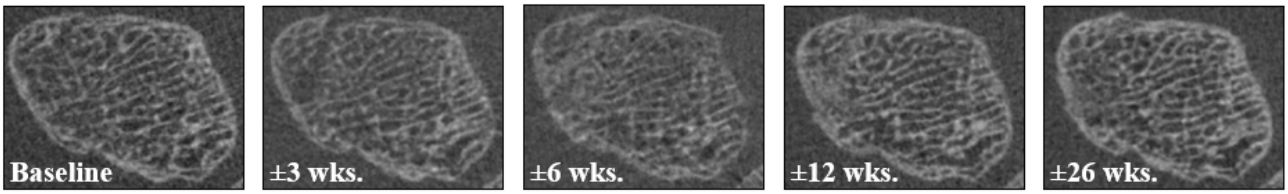


*Fig. 1: Slices of an HR-pQCT scan showing the healing of a scaphoid fracture until 26 wks. after initial presentation.*

CONCLUSION: The healing of conservatively-treated scaphoid fractures appears to start with a decrease in bone mineral density, trabecular thickness, and ultimate force until six weeks after initial presentation and a subsequent stabilization or increase. There appears no densitometric, microarchitectural, and bone biomechanical restoration to baseline yet at 26 weeks after initial presentation.

SPONSOR: Research foundation of VieCuri Medical Center Noord-Limburg, The Netherlands (Funding no. E.18.31.031-4).
DISCLOSURE STATEMENT: Bert van Rietbergen is an external consultant for Scanco Medical AG.
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# $T_2$ CLUSTER ASYMMETRY DETECTS EARLY CHANGES IN ACL-INJURED CARTILAGE

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INTRODUCTION: Cluster analysis has been able to identify development over time of focally elevated quantitative MRI $T_2$ values following ACL-injury[1]. While this approach identifies longitudinal relative to a baseline scan, it would be advantageous to obtain quantitative measures of osteoarthritis from a single scan. As gait asymmetry has been shown to be present in mild knee OA[2], we hypothesized that clusters of T2-asymmetry may similarly be able to detect inter-knee differences indicative of OA.

OBJECTIVE: To determine if the extent of $T_2$ asymmetry clusters differs between ACL-injured subjects and healthy controls.

METHODS: 10 ACL-reconstruction subjects (5W/5M, 39±12 yrs, BMI: 23±1.5) and 8 controls (2W/6M, 39±15 yrs, BMI: 25±3.4) were included. The ACL-reconstructed and contralateral knees were scanned separately at: 3 weeks, 3, 9, and 18 months post-surgery. Both knees of the controls were scanned at one time point. A qDESS sequence (5-minutes/knee) was acquired to calculate $T_2$ relaxation times the two qDESS echoes[3]. Femoral cartilage $T_2$ projections were created by fitting a cylinder (axis medial-to-lateral) to the segmented cartilage and radially projecting T2 data [1]. Deep and superficial cartilage layers were created by dividing cartilage at the midpoint. Difference maps were created by subtracting the medial-lateral reversed contralateral (left knee for controls) cartilage $T_2$ projection maps from the ACL-injured (right knee for controls). Asymmetry $T_2$ clusters in these difference maps were quantified as a contiguous set of pixels with an area greater than 12.4mm$^2$ consisting of absolute values greater than twice the standard deviation of the control subjects' asymmetry difference maps[1][Fig. 1]. Our outcome was reported as the change in $T_2$ asymmetry percent cluster area ($\Delta T2\%CA_{ASYM}$), defined as the area of all positive clusters (increased $T_2$, $\Delta T2\%CA_{ASYM+}$) and negative clusters (decreased $T_2$, $\Delta T2\%CA_{ASYM-}$) as a percentage of the total femoral cartilage area. To further characterize patterns of asymmetry in only ACL-reconstructed subjects, the $\Delta T2\%CA_{ASYM+}$ (increased $T_2$ clusters) and $\Delta T2\%CA_{ASYM-}$ (decreased T2 clusters) relative to the contralateral knee were separately analyzed at each time-point.

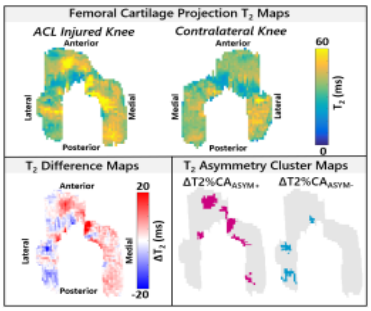


**Fig. 1**: (Top) Sample T2 projection maps femoral superficial cartilage of an ACL-injured and contralateral knee 3-months post-surgery and (bottom) resulting T2 difference maps and the positive ($\Delta T2\%CA_{ASYM+}$) and negative ($\Delta T2\%CA_{ASYM-}$) clusters maps.

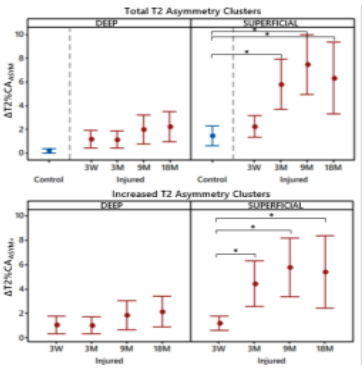


**Fig 2**: (Top) $\Delta T2\%CA_{ASYM}$ results for ACL-injured subjects at: 3-weeks (3W), 3-months (3M), 9-months (9M) and 18-months (18M) post-surgery compared to controls. (Bottom) $\Delta T2\%CA_{ASYM+}$ (increasing T2) results in the ACL-injured subjects comparing changes between time-points. *P<0.05.

RESULTS: The $\Delta T2\%CA_{ASYM}$ was higher in ACL-injured subjects' knees at 3, 9, and 18 months post-surgery compared to control knees in the superficial layer (P=0.002, P<0.001 and P=0.00). There were no significant differences between the $\Delta T2\%CA_{ASYM}$ of the deep layer at any time compared to the control knees (P>0.999). For the increased T2-change cluster analysis in the ACL-injured subjects, the $\Delta T2\%CA_{ASYM+}$ was significantly higher in the superficial layer at 3, 9 and 18-months relative to 3-weeks (P=0.006, P<0.001, and P=0.001)[Fig. 2]. For the negative cluster analysis in the ACL-injured subjects ($\Delta T2\%CA_{ASYM-}$), the time-point factor was not a significant term in the model and $\Delta T2\%CA_{ASYM-}$ remained very low.

CONCLUSION: By focusing on the surface layer and looking at differences vs. the contralateral knee at a single time-point, this asymmetry method is potentially a clinically feasible single-time-point protocol for detecting early OA. Use of the contralateral knee as an internal reference shows promise in detecting early OA changes without the need for longitudinal data.

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DISCLOSURES: AC has consulted for Skope MR, Subtle Medical, Chondrometrics.
REFERENCES: 1. Monu, OA&C 2017, 2. Mills, Phys. Med. Rehab. 2013, 3. Sveinsson, MRI 2017
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**MICROARCHITECTURE OF HETEROTOPIC OSSIFICATION IN FIBRODYSPLASIA OSSIFICANS PROGRESSIVA: AN HR-PQCT CASE SERIES**

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INTRODUCTION: Fibrodysplasia ossificans progressive (FOP) is a rare disease characterized by the formation of heterotopic ossification (HO) in ligaments, tendons, and muscles. Invasive techniques to investigate mature HO are contraindicated as these trigger the formation of HO. The high-resolution peripheral quantitative computed tomography (HR-pQCT) is a non-invasive technique that could potentially be used to examine the microarchitecture of HO.

OBJECTIVE: This case study aimed to assess mature HO in FOP with HR-pQCT and to explore whether the HO is microarchitecturally resembling normal skeletal bone of FOP and the skeletal bone of an age- and gender-matched reference.

METHODS: HR-pQCT scans (61-µm isotropic voxel size) were acquired of peripherally-located HO and standard distal radius and tibia regions in two adult FOP-patients, both with the classical mutation (p.R206H). Standard analyses were performed to quantify bone mineral density and trabecular and cortical microarchitecture, and micro-finite element analysis was used to estimate ultimate force. The parameters were compared between HO and neighboring distal radius or tibia and with an age- and gender-matched normative dataset from literature.

RESULTS: HO was located around the halluces and ankles and in the Achilles tendon. Qualitative assessment of HO located around the halluces and ankles revealed coalescence with its neighboring skeleton. A neocortex was formed, and the original skeletal cortex was partially replaced with trabeculae. HO located in the Achilles tendon was isolated from neighboring skeletal bone (Fig. 1) and showed quantitatively a low total and trabecular density and cortical thickness compared to normative tibia data. Trabecular microarchitecture, in contrast, was comparable to that of the normative tibia data. The tibiae of both patients also had a low total and trabecular density and cortical thickness compared to the normative data, but also trabecular microarchitecture deviated considerably from this normative data. Ultimate force was comparable between the isolated HO and the neighboring tibia when accounting for areal differences.

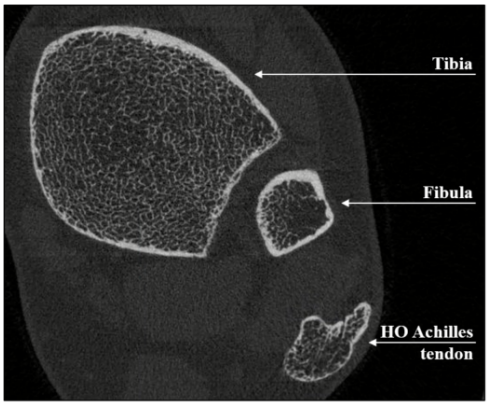

*Fig. 1: Slice of an HR-pQCT scan showing isolated HO in the Achilles tendon of one FOP-patient.*

CONCLUSION: HR-pQCT allows detailed assessment of peripherally-located HO in FOP-patients and can provide new insights into the microarchitecture of mature HO and skeletal bone in this extremely rare disease.

SPONSOR: None.
DISCLOSURE STATEMENT: Bert van Rietbergen is an external consultant for Scanco Medical AG. The other authors do not declare a conflict of interest.
ACKNOWLEDGEMENT: The two FOP-patients are thanked for their participation.
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**INTER- AND INTRARATER RELIABILITY OF A KNEE OSTEOARTHRITIS MACHINE LEARNING DECISION-AID ALGORITHM WITH HUMAN INTERPRETERS IN A NEAR-CLINICAL SETTING**

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INTRODUCTION: Overall increase in medical imaging, scarcity of radiologist and concerns on interrater variability have sparked efforts to develop time saving and robust auto-reporting. Plain radiography remains part of mainstay diagnostic workup for knee osteoarthritis (KOA). Radiobotics' RBknee is a CE-marked decision-aid deep learning based software for automated description of radiographic KOA including Kellgren-Lawrence (KL) grading.

OBJECTIVE:
1-Does RBknee have similar interrater reliability with musculoskeletal radiologists as they have with each other?
2-Does RBknee have better intrarater reliability compared to musculoskeletal radiologists?

METHODS: In this method comparison study, two musculoskeletal radiology consultants, two experienced reporting radiographers, two resident radiologists and RBknee rate both knees of 50 plain radiographs (n=100). All exams are extracted in an anonymous way from the clinical production PACS at Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. Exams are posterior-anterior projection, weight-bearing and referred for KOA evaluation. Radiographs are randomly selected. Before rating, each reader was given an atlas on KL grades (based on OAI KOA classifications), exemplifying the presentations of various grades. Each human reader independently rates each knee on the ordinal KL grade. RBknee outputs a categorical grade. Quadratic weighted kappa is calculated as a metric for interrater reliability. Results of human readers are pooled as all human readers (ties deferring to the most experienced radiology consultant), musculoskeletal radiologists, junior radiologists, and reporting radiographers. For intrarater reliability, the order and names of studies were randomized. After at least four weeks of washout all readers repeated KL grading.

RESULTS: One knee radiograph was excluded on basis of poor quality. RBknee showed good-to-excellent interrater reliability with all human readers: (0.84-0.90 (CI95%: 0.79-0.89 and 0.87-0.94) compared to radiology consultants; 0.82-0.85 (CI95%: 0.77-0.88 and 0.80-0.91) compared to reporting radiographers; 0.85-0.85 (CI95%: 0.80-0.90 and 0.80-0.90) compared to radiology residents). RBknee agreement with a consensus among all human readers was 0.89 (CI95%: 0.84-0.93). Interrater reliability among musculoskeletal consultants was 0.89 (CI95%: 0.86-0.93).
Intrarater reliability for consultants: 0.96 (CI95%: 0.94 - 0.98) and 0.94 (CI95%: 0.91 - 0.97), for reporting radiographers: 0.85 (CI95%: 0.78 - 0.92) and 0.84 (CI95%: 0.79 - 0.90), and for junior radiologists: 0.92 (CI95%: 0.89 - 0.95) and 0.86 (CI95%: 0.81 - 0.91), for RBknee: 1 (CI95%: 1-1)

CONCLUSION: RBknee showed good-to-excellent interrater reliability compared with human experts in KL grading of KOA. Agreement among musculoskeletal consultants was not statistically different from each consultant's agreement with RBknee. Interrater reliability was not different among consultants, reporting radiographers and junior radiologists. The high level of interrater reliability on a dataset from a clinical environment supports the use of decision-aid algorithms like RBknee as a clinical tool. Though all readers had surprisingly high intrarater reliability, none could match the level of RBknee, which is to be expected since RBknee deterministic.
Next steps will be to test intrareader reliability after at least 4 weeks of washout as well as RBknee's ability to grade osteophytes on the lateral projection.

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DICLOSURE STATEMENT: M. Axelsen and M. Brevadt are employees of Radiobotics ApS. M. Boesen is a member of the scientific advisory board at Radiobotics.
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**KNEE CARTILAGE THICKNESS OF ACL-INJURED NON-COPERS & COPERS: A 1-YEAR STUDY**

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INTRODUCTION: ACL injury patients can be classified as non-copers (NC) or copers (COP). NC have persistent dynamic knee instability with daily activities; COP can dynamically stabilize their knee and resume preinjury activities. NC have worse clinical presentation and movement patterns than COP. Given the role of joint loading in cartilage degradation, NC/COP status may distinguish between those who do and do not develop knee OA. Yet, no work has compared cartilage outcomes of NC and COP.

OBJECTIVE: To test the hypothesis that knee cartilage thickness of ACL injured patients and its change over 1 year differ between NC and COP.

METHODS: NC [n=12 (10 women), age 43.8±9.6 y, body mass index (BMI) 25.6±5.3 kg/m$^2$] and COP [n=15 (6 women), age 34.1±8.8 y, BMI 25.7±5.8 kg/m$^2$] were studied. Patients were classified as NC if they met at least 2/3 of the following criteria: >1 episode of giving way in the last 6 months; <85/100 points on the Lysholm Knee Score; and limb symmetry index <85% for a single leg hop test. NC completed a 3-month intervention comprising lower-limb strength training and neuromuscular re-education. COP received conservative treatment, as recommended by their healthcare provider. A control group (CON) [n=14 (10 women), age 42.6±9.2 y, BMI 24.8±3.0 kg/m$^2$] of persons without past lower-limb injury/surgery or known lower-extremity conditions was used as a reference. Baseline (BL) and ~1-year follow-up (FU) knee MRI scans were acquired using a 3D VIBE sequence with water excitation (1.5T, Avanto, Siemens; 0.3125 x 0.3125 x 1.5 mm resolution). The weight-bearing tibiofemoral cartilage plates were manually segmented by experienced readers. Cartilage thickness was computed in 16 sub-regions, 3 per femoral condyle (internal, central, external) and 5 per tibial condyle (internal, central, external, anterior, posterior). Repeated measures analyses of variance tested the effects of group, time and group*time interaction across outcomes, adjusting for sex. Post-hoc Tukey tests were used as appropriate ($\alpha$=0.05). Assumptions were confirmed and outliers scrutinized.

RESULTS: COP were younger than NC (p=0.024) and CON (p=0.042). Groups were not different in terms of sex (p=0.052), BMI (p=0.874) and time between injury and BL (NC 6.1±3.2 months; COP 5.6±2.6 months; p=0.664). One outlier (NC) whose values were consistently higher across cartilage outcomes (i.e., >1.5 times the interquartile range above the third quartile) was removed to not distort the results. Cartilage in the central lateral tibia was thinner at both time points in NC (BL 2.89±0.66 mm; FU 2.90±0.62 mm) than in COP (BL 3.36±0.39 mm, p=0.003; FU 3.38±0.38 mm, p=0.002) and CON (BL 3.38±0.50 mm, p=0.002; FU 3.38±0.48 mm, p=0.002). Cartilage in the external lateral tibia was also thinner at both time points in NC (BL 1.54±0.36 mm; FU 1.54±0.36 mm) than in COP (BL 1.80±0.24 mm, p=0.002; FU 1.83±0.23 mm, p=0.001) and CON (BL 1.73±0.25 mm, p=0.017; FU 1.74±0.29 mm, p=0.013). Compared to CON (BL 2.73±0.52 mm; FU 2.66±0.45 mm), NC (BL 2.02±0.37 mm, p<0.001; FU 2.01±0.37 mm, p<0.001) and COP (BL 2.32±0.41 mm, p=0.015; FU 2.34±0.42 mm, p=0.050) had thinner cartilage at both time points in the internal lateral tibia. Finally, COP showed an increase in cartilage thickness of 0.07±0.09 mm (p=0.001) in the weight-bearing central medial femur over 1 year.

CONCLUSION: NC inherently had thinner cartilage in the lateral tibia, which may influence dynamic knee loading and contribute to persisting joint instability. COP had increased thickness in the weight-bearing central medial femur, confirming prior ACL injury studies showing that cartilage "thickening" may precede thinning as part of the early OA process – particularly in this sub-region. Future work should examine the link between dynamic knee loading and cartilage outcomes in NC and COP.

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**IMPROVING KNEE PAIN AND GAIT CORRELATE TO INCREASING CARTILAGE T2 FOLLOWING PLATELET RICH PLASMA TREATMENT OF EARLY KNEE OA**

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INTRODUCTION: There is high clinical and consumer interest in treatment of knee OA with autologous platelet rich plasma (PRP). Clinical results have been mixed with leukocyte poor PRP showing early evidence suggestive of symptomatic improvement. Even less is known about the effects of intra-articular PRP injections on knee mechanics and articular cartilage.

OBJECTIVES: To determine if improvements in knee pain and function and walking mechanics following PRP treatment for symptomatic early knee OA are associated with concurrent longitudinal improvements to cartilage structure demonstrated by decreased T2 values.

METHODS: Twenty human-subjects with symptomatic early knee OA (14 males, age: 56.4±10.4 years; BMI: 29±4 kg/m2; Pain 4/10 or higher, KL grade: 2.0±1.0) participated in this IRB-approved study. Prior to PRP treatment and again at 6 months after last treatment, veterans completed WOMAC questionnaires, underwent gait analysis and 3T knee MRI. PRP treatment consisted of a series of three injections (3.5-4 ml) of autologous leukocyte poor PRP received approximately one week apart. Ambulatory speed, peak vertical ground reaction force (GRF), and first peak total joint moment (TJM) were calculated from 3 walking trials. TJM was calculated as the square root of the sum of the squares of the knee adduction, flexion, and rotation moments. T2 maps were acquired using a 2-D fast spin echo sequence with 8 echo images, TEs ranging 5-70ms and TR=1500ms. Four regions of interest (ROIs) were manually segmented from single sections to evaluate full-thickness cartilage to the center weight-bearing portions of the medial and lateral femoral condyles and tibial plateaus (MFC, LFC, MTP, LTP). Paired t-tests assessed longitudinal changes in WOMAC scores, gait metrics and cartilage T2; statistical significance was accepted for $p<0.05$. Pearson correlations assessed the relationships between longitudinal WOMAC changes (6 month – baseline) and concurrent gait changes (6 month – baseline) and between longitudinal gait changes and concurrent T2 changes. Bonferroni adjustment corrected for multiple comparisons; statistical significance was accepted for $p<0.017$).

RESULTS: Cartilage T2, averaged across all 20 subjects, decreased significantly in 2 of the 4 cartilage regions examined between baseline and 6-months after completion of PRP treatments. T2 decreased 2.4%, 3.6% in MTP, LFC cartilage regions (mean differences=-1.33, -1.05ms; $p=0.006$, 0.018). T2 showed a trend for a 3.7% decrease in MFC cartilage (mean difference=-1.4ms, $p=0.086$) but did not change in LTP cartilage ($p>0.79$). Neither mean WOMAC nor mean gait assessments changed significantly over time. On an individual basis, improvements in WOMAC knee pain between baseline and 6-months post-PRP treatment were associated with increases in GRF (R=0.55, $p=0.013$) over the same time. Additional trends for associations between improving WOMAC scores and GRF, TJM and speed were observed, but these relationships were not significant after adjustment for multiple comparisons. Increasing GRF (R=0.74, $p<0.0005$), TJM (R=0.66, $p=0.001$), and walking speed (R=0.58, $p=0.007$) were associated with concurrent increases in LTP T2 values. Further, there was a trend for increasing TJM with increasing LFC cartilage T2 (R=0.43, $p=0.061$).

CONCLUSION: T2 mapping showed longitudinal improvements (*i.e.* decreases) to knee cartilage composition in some, but not all, regions and subjects following PRP treatment. Interestingly, patients who increased knee loading after PRP treatment showed concurrent increases to lateral tibial cartilage T2 values, suggestive of worsening subsurface cartilage degeneration. These findings suggest that a reduction in pain leading to greater knee joint loading may accelerate cartilage matrix degeneration. Thus, pain relief, without concurrent interventions to reduce joint loading, may lead to more rapid disease progression in patients with early knee OA. Furthermore, these intriguing findings lend further support to the potential utility of T2 mapping for evaluation of joint cartilage changes in clinical trials involving patients with early knee OA.

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**MDCT ARTHROGRAPHY ASSESSMENT OF CARTILAGE AND SCAPHOLUNATE DISSOCIATION REGARDING SPECIFIC-COMPONENT TEARS OF THE SCAPHOLUNATE LIGAMENT**

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INTRODUCTION: Untreated post-traumatic scapholunate interosseus ligament (SLIL) injury may lead to the development of a specific pattern of progressive wrist osteoarthritis known as SLAC (scapholunate advanced collapse), one of the most frequent patterns of wrist osteoarthritis. The dorsal component of SLIL is known to be the strongest and main responsible for scapholunate stability, as demonstrated in previous cadaveric studies. No previous study has evaluated the distribution and severity of cartilage damage and scapholunate dissociation considering component-specific tears of the SLIL, using an imaging technique where we can directly assess both cartilage and SLIL morphology.

OBJECTIVE: To evaluate the distribution and severity of cartilage damage and scapholunate dissociation assessed on multi-detector computer tomography (MDCT) arthrography in a sample of patients with SLIL injury, regarding component-specific tears.

METHODS: In this cross-sectional, retrospective study, we searched for the clinical and radiological records of patients who were referred to the radiology department to undergo MDCT arthrography of the wrist from 2012 to 2015. Patients were included if they had a history of wrist trauma associated with chronic wrist pain, with unequivocal findings of rupture of the SLIL on MDCT arthrography. Two musculoskeletal radiologists independently assessed the MDCT arthrography images. Morphology of SLIL dorsal and volar components was graded as: normal, partial, or complete tear. Quantitative assessment of the scapholunate dissociation was performed using the coronal image at the bi-styloid plane with measurements performed using the tenth of a millimeter. Cartilage damage was assessed in 14 distinct regions of the wrist using a semiquantitative WORMS-modified scoring system (from 0 to 6). For each patient, the “global”, the “degenerative”, and the “radial” scores of cartilage damage were obtained by summing all the modified WORMS scores using different definitions. We assessed if cartilage severity was greater in patients having complete tears of the dorsal component of the SLIL compared to patients without complete tears of the same component. We did the same comparison considering involvement of the volar component of the SLIL. The same groups were compared regarding scapholunate dissociation severity. The Student's t-test and the Wilcoxon Rank-Sum test were used to compare the different groups adjusting for the presence of concomitant dorsal and volar component tears.

RESULTS: Forty-three patients were finally included in our sample (mean age was 29.5 ± 10.6 (range 19 to 72), 65.1% (N=28) were male). The intra-reader reliability for the assessment of dorsal and volar components of the SLIL was 1.0 and 0.91, respectively. The inter-reader reliability for the same features was 0.85 and 0.72, respectively. Depending on specific regions, intra-reader reliability for the modified WORMS scores varied between 0.55 to 1.0, while the inter-reader reliability varied between 0.45 and 0.82. The cartilage damage scores obtained were greater in patients with complete SLIL dorsal component tears than in other patients, with no significant differences in cartilage scores when considering complete SLIL volar component tears. Scapholunate dissociation was greater in patients exhibiting complete SLIL dorsal component tears (mean 5.02mm; 95%CI 4.21, 5.83) vs. patients without complete SLIL dorsal component tears (mean 2.89mm; 95%CI 2.35, 3.44), $p<0.0001$. Scapholunate dissociation was also greater in patients with SLAC wrist ($p<0.0001$), with a cut-off value of 3.9 mm for diagnosing SLAC (sensitivity 79, 2% and specificity 94.7%).

CONCLUSION: In this sample of non-surgically treated patients with SLIL injury assessed on MDCT arthrography, we showed that complete tears of the dorsal component of the SLIL were independently associated with greater schapholunate dissociation and cartilage damage, suggesting in vivo that the dorsal component represents the most important component of the SLIL in scapholunate (and carpal) stability.

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**THE RELATIONSHIP BETWEEN THE POSTERIOR RADIOSCAPHOID ANGLE AND THE SEVERITY OF CARTILAGE DAMAGE AND SCAPHOLUNATE DISSOCIATION AFTER SCAPHOLUNATE LIGAMENT TEARS**

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INTRODUCTION: Post-traumatic scapholunate interosseous ligament (SLIL) tears may lead to scapholunate dissociation, especially when associated with extrinsic ligament injury. Dorsal intercalated segment instability (DISI) is responsible for abnormal joint kinematics and excessive loading through the radial side of the wrist joint, leading to degenerative arthritis at the radioscaphoid joint, followed by carpal collapse, and midcarpal osteoarthritis (scapholunate advanced collapse - SLAC - wrist). DISI would theoretically increase the posterior radioscaphoid angle (PRSA) assessed on multi-detector computed tomography (MDCT).

OBJECTIVE: To evaluate the relationship of the PRSA measurements with the severity of cartilage damage and scapholunate dissociation in patients with SLIL tears who underwent MDCT arthrography, including establishing a pathological threshold value for the PRSA capable of detecting a SLAC wrist.

MATERIALS: We retrospectively included 34 consecutive patients with SLIL tears detected on multi-detector computed tomography (MDCT) arthrography. We further included 34 consecutive patients having post-traumatic chronic wrist pain who underwent MDCT arthrography, which demonstrated no post-traumatic ligament or bone pathology, including the SLIL. Patients were excluded if they had surgical treatment before MDCT arthrography, an associated ligament injury depicted on MDCT arthrography, any wrist fracture, chondrocalcinosis, or any congenital conditions or anatomical variations. Two musculoskeletal radiologists assessed the MDCT arthrography images. In equivocal cases, a consensus reading was performed with a third musculoskeletal radiologist with 20- years of experience. PRSA was measured on sagittal reformatted images after identifying the image depicting the posterior-most point of the scaphoid. A line passing through the dorsal and volar rims of the scaphoid fossa of the radius was drawn on this image. Then, a second line was drawn, passing through the dorsal rim of the radius and the posterior-most point of the scaphoid. The angle between these lines was designated the PRSA. Morphology of SLIL components was graded as: normal, partial, or complete tear. Quantitative assessment of the scapholunate dissociation was performed using the coronal image at the bi-styloid plane with measurements performed using the tenth of a millimeter. Cartilage damage was assessed in 14 distinct regions of the wrist using a semiquantitative WORMS-modified scoring system (from 0 to 6). For each patient, the “global”, the “degenerative”, and the “radial” scores of cartilage damage were obtained by summing all the modified WORMS scores using different definitions. SLAC staging for each patient (from 1 to 3) was based on the distribution of cartilage damage seen on MDCT arthrography (SLAC grade 0 meaning no associated cartilage damage). Variance analyses with multiple comparisons (multiple tests) and correlation analysis (Pearson) were used to assess the relationships between the PRSA and severity of cartilage damage and scapholunate dissociation in different groups.

RESULTS: A total of 68 patients were included: 34 patients with SLIL tears (mean age 39.3 years for patients with SLAC 0 [SD 9.8; 95%CI 32.0, 47.5], and 43.7 years for patients with SLAC≥1 [SD 11.9; 95%CI 36.7, 55.3] and 34 controls (mean age 33.4 years [SD 10.2; 95%CI 27.0, 39.3]). Thirty-eight patients in total were male (55.9%). The PRSA was greater in patients with SLAC≥1 (mean value 113.4°; SD 7.1; 95%CI 107.9, 118.0) than in patients with SLAC 0 (mean value 106.9°; SD 9.2; 95%CI 99.6, 114.4; p=0.022) or in controls (mean value 104.6°; SD 5.0; 95%CI 101.2, 108.1; p<0,001). We found a cut-off value of 114.1 ° of the PRSA for diagnosing SLAC≥1 (sensitivity 61.1% and specificity 75%). Furthermore, PRSA was moderately and positively correlated with summed modified WORMS scores for cartilage damage for global (0.47), degenerative (0.46), and radial (0.51) scores (p<0.01). Finally, there was a positive but weak correlation between the PRSA and scapholunate dissociation (0.36; p=0.04).

CONCLUSION: The PRSA was significantly higher in SLAC wrist and was positively correlated with the severity of cartilage damage and scapholunate dissociation. Whenever direct cartilage assessment of the wrist is not possible is cases where post-traumatic ligament injury is suspected (as in standard MCDT without arthrography), the assessment of such angle may potentially identify patients at risk for developing SLAC. Further prospective and longitudinal studies are needed to confirm the predictive value of PRSA.

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**THE IMPACT OF A SIGNIFICANT WEIGHT LOSS ON INFLAMMATION ASSESSED ON DYNAMIC CONTRAST-ENHANCED MRI AND STATIC MRI IN KNEE OSTEOARTHRITIS: A PROSPECTIVE COHORT STUDY**

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INTRODUCTION: Obesity is a worldwide health issue and one of the most important risk factors for development of osteoarthritis (OA). The beneficial clinical effect of weight loss is well documented and weight loss is recommended (where appropriate) as core treatment in OA. However, the exact mechanisms causing this effect are not well understood. Inflammation has been proposed as a possible link between OA and overweight and studies have found that weight loss lowers biomarkers of inflammation. Dynamic contrast-enhanced (DCE) MRI involves acquisition of MR images in rapid succession before, during and after an intravenous injection of a contrast agent. It allows an evaluation of the perfusion, vascularity, and capillary permeability in the tissue and provides measurements of the extent of inflammation.

OBJECTIVE: To study the impact of weight loss on inflammation in individuals with overweight and knee osteoarthritis (OA) using both static- and dynamic contrast-enhanced (DCE)-MRI and assess the association of these changes to pain.

METHODS: Individuals with overweight (BMI > 27) and knee OA were examined before and after a >5% weight loss over 8 weeks (ClinicalTrials.gov NCT02905864). Using 3-T MRI, inflammation was quantified from non-contrast enhanced static-MRI according to MOAKS and contrast enhanced static MRI according to BLOKS and 11-point whole-knee synovitis score. DCE-MRI was used to assess the inflammation in the infra patellar fat pad (IPFP). Pain was assessed using KOOS.

RESULTS: Complete data were available in 117 participants with a mean age of 60 years, BMI of 35 kg/m2 and KOOS pain score of 64. Mean weight loss was 12 kg and KOOS pain was improved by 13 points at follow-up. Change in inflammation was not associated with weight loss in static MRI. None of the MRI variables correlated with the change in KOOS pain.

CONCLUSION: Weight loss did not induce a significant change in inflammation in individuals with overweight and OA. The significant clinical beneficial effect of weight loss on knee pain in individuals with overweight and knee OA seems uncoupled to changes in imaging markers of synovitis.

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**PREVALENCE OF SMALL OSTEOPHYTES ON KNEE MRI IN SEVERAL LARGE CLINICAL AND POPULATION-BASED STUDIES OF VARIOUS AGE GROUPS AND OA RISK FACTORS**

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INTRODUCTION: Osteophytes, also small ones, are an important imaging feature of OA. Attributable to the increased application of MRI, a large number of early OA features, including osteophytes, are detected, even in populations without OA. The question arises whether these are truly pathophysiologic features of early OA or rather a result of physiologic ageing or a merely transient phenomenon.

OBJECTIVE: The aim of this study is to explore the prevalence of osteophytes on MR in various locations of the knee, with special emphasis on small osteophytes, across multiple large studies conducted in our institution comprising a wide range of subjects with different ages and OA risk factors.

METHODS: This is a retrospective study comprising study subjects of four different studies: the Triple P study of patients with patellofemoral pain and healthy control subjects, the KNALL study of patients with an anterior cruciate ligament lesion, the PROOF study in overweighed females, and a subgroup of the population-based Rotterdam Study in middle-aged women. For all studies baseline MRI's were included, one knee in the case of Triple P and KNALL and both knees for PROOF and Rotterdam Study. Osteophytes were scored at non-fat saturated, intermediate weighted sequences according to MOAKS by a set of readers trained by an experienced musculoskeletal radiologist. If osteophytes were scored in a similar fashion was checked visually in a subset of MRI's in a consensus meeting. Cross-tabulations were used to explore the prevalence of osteophytes, particularly grade I osteophytes, across studies. GEE models were applied to analyse the overall prevalence across different ages groups, BMI categories and gender.

RESULTS: 2425 knee MRI's were included. Osteophyte grading appeared similar across studies in the consensus meeting (Figure 1). A large number of grade 1 osteophytes were found in all four studies. The largest number of osteophytes were present in the youngest age group of <30 years (69,6%) compared to 36.8% when ≥30<50 years and 54,3% when ≥50 years. In the youngest age group, most were grade 1 osteophytes (87%). No trend was present for gender. A small positive trend was observed for BMI, in which a higher BMI was correlated with grade 2 and 3 osteophytes and with the number of grade 1 osteophytes

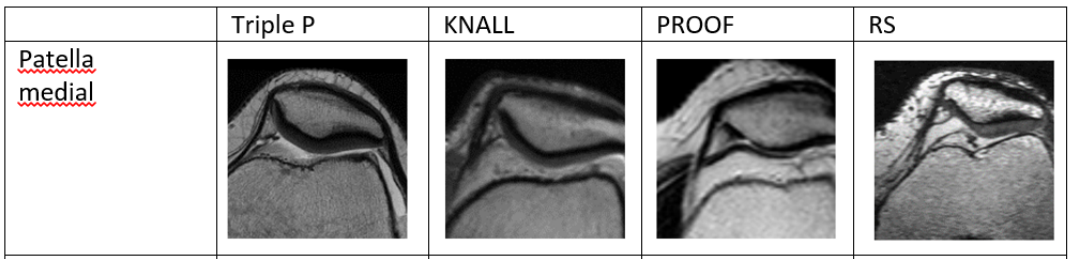


**Figure 1.** Appearance of grade 1 osteophyte across studies. Medial patella as an example.

CONCLUSION: Small osteophytes are highly prevalent among populations with varying age and OA risk factors, in particular among young subjects without other OA features. This suggest that these "osteophytes" do not necessarily represent early OA, but rather indicate a transient physiologic phenomenon.

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**THE ROLE OF INFRAPATELLAR FAT PAD IN KNEE OSTEOARTHRITIS**

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INTRODUCTION: The infrapatellar fat pad (IPFP) is an intra-capsular but extra-synovial tissue, which accommodates the changing volume and shape of irregular articular spaces during joint movement and may play an active role in knee OA.

OBJECTIVE: To determine if the size and quality alteration of IPFP are associated with structural changes and symptoms in knee osteoarthritis.

METHODS: 1) The maximal IPFP area was measured using T2-weighted fat-suppressed MRI in 356 community-dwelling male and female adults aged 50-80 years at baseline and approximately 2.6 years later. 2) The IPFP volume was measured using fat-suppressed 3-D T1-weighted spoiled gradient recall MRI in 174 patients with clinical knee OA (mean age, 55.5 years). 3) The hyperintensity alteration (0-3) of IPFP was measured using T2-weighted fat suppressed MRI in 874 subjects (mean 62.1 years, 50.1% female) selected randomly from local community at baseline and 770 were followed up (only 357 had MRI at follow-up) over 2.6 years. 4) Quantitative hyperintensity alteration of IPFP was measured using T2-weighted MRI at P0 (the visit when incident radiographic OA was observed on a radiograph), P1 (1 year prior to P0), and baseline. Case knees (n = 355), as defined by incident radiographic OA, were matched 1:1 with control knees, in a nested case-control design. 5) The hypointensity alteration (0-3) of IPFP was measured using T2-weighted fat suppressed MRI in 874 subjects selected randomly from local community and followed up 2.7 years later (range 2.6-3.3 years).

RESULTS: 1) IPFP maximal area in women was significantly and negatively associated with changes in knee pain (β: -0.18 to -0.86 for total knee pain, pain at night while in bed, pain when sitting/lying and pain when standing upright, all $p<0.05$). IPFP maximal area in women was beneficially associated with change in tibial cartilage volume per annum (β: +1.56% per $cm^2$ at medial site; +0.86% per $cm^2$ at lateral site, both $p<0.05$). 2) Greater IPFP volume was associated with greater tibial and patellar cartilage volume (all $p < 0.05$), and fewer cartilage defects at all sites (OR 0.88-0.91, all $p < 0.05$). IPFP volume was associated with presence of BML at lateral tibial and medial femoral sites (OR 0.88-0.91, all $p < 0.05$) and osteophytes at lateral tibiofemoral compartment (OR 0.88, $p < 0.05$). 3) Baseline signal intensity alteration within IPFP was significantly and positively associated with increases in knee pain when going upstairs/downstairs as well as increases in tibiofemoral cartilage defects and BMLs, and negatively associated with change in lateral tibial cartilage volume. 4) Baseline IPFP measures including the mean value and standard deviation of IPFP signal intensity, the mean value and standard deviation of IPFP high signal intensity, median and upper quartile values of IPFP high signal intensity, and the clustering effect of high signal intensity were associated with incident knee radiographic OA over 4 years. 5) Baseline hypointensity alteration was significantly and positively associated with increases in knee cartilage defects (OR: 2.27, 95 % CI: 1.61-3.21), BMLs (OR: 1.91, 95 % CI: 1.39-2.62), and knee pain (OR: 1.36, 95 % CI: 1.05-1.76).

CONCLUSION: The size of IPFP, represented by both in maximal area and volume, showed a protective role in knee OA. The quality alterations of IPFP including hyperintensity and hypointensity alterations, measured using both semi-quantitative and quantitative measures, showed a detrimental role in knee OA. Therefore, the size and quality alteration of IPFP may play different roles in knee OA.

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**EFFECT OF TRAINING SET SAMPLE SIZE ON THE AGREEMENT, ACCURACY, AND SENSITIVITY TO CHANGE OF AUTOMATED U-NET-BASED CARTILAGE THICKNESS ANALYSIS COMPARED WITH MANUAL EXPERT SEGMENTATION**

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INTRODUCTION: Automated cartilage segmentation using U-Net architectures and convolutional neural networks (CNNs) has shown promising results. We recently observed training models specific to the radiographic disease stage (KLG) to be superior to more general training models that contained various radiographic stages (Wisser et al., same conference). However, it is currently unknown, how the sample size of the training model affects U-net measurement performance.

OBJECTIVE: To systematically study the effect of training data set sample size on the agreement, accuracy, and sensitivity to change in automated medial femorotibial compartment (MFTC) cartilage thickness analysis, in knees with medial radiographic OARSI JSN grade 2.

METHODS: We examined a total of 371 knees from 371 Osteoarthritis Initiative (OAI) participants that had expert manual segmentation of the MFTC cartilages. All knees (52% female; age 63.2±8.8y; BMI 30.2±4.8) displayed medial OARSI JSN grade 2 (centralized readings at Boston University). The test set contained 23 knees (57% female; age 60.6±7.5y; BMI 31.4±4.8). The training data sets contained 10, 25, 2 x 25 (baseline and 1y follow-up), 50, 100, 175, 250, and 325 knees, respectively. The validation set included 23 knees. Each smaller training data set represented a subset of the larger data set. The Dice Similarity Coefficient (DSC) between automated and manual segmentation was used as a measure of agreement, the correlation of cartilage thickness analysis as a measure of accuracy, and the standardized response mean (SRM = mean/SD change) over 1 year as a measure of sensitivity.

RESULTS: The sample size of the training set had a surprisingly small effect on the performance of the U-Net (Table 1). All training model sizes led to larger SRMs than manual expert segmentation, except for the n=025 model (Table 1). Adding 25 follow-up to 25 baseline data sets increased the sensitivity to change from -0.30 to -0.61; the greatest SRM was observed for 50 baseline data sets (0.66).

**Table 1: Effect of training set sample size on automated segmentation performance**

| | DSC | Correlation (r) | Mean Change µm | SD Change | SRM |
|---|---|---|---|---|---|
| **Manual** | | | -129 | 293 | -0.44 |
| **n=010** | 0.84 | 0.89 | -116 | 222 | -0.52 |
| **n=025** | 0.85 | 0.88 | -74 | 248 | -0.30 |
| **n=2x25** | 0.85 | 0.90 | -105 | 171 | -0.61 |
| **n=050** | 0.86 | 0.90 | -121 | 183 | -0.66 |
| **n=075** | 0.86 | 0.91 | -90 | 164 | -0.55 |
| **n=100** | 0.86 | 0.89 | -100 | 181 | -0.55 |
| **n=175** | 0.86 | 0.90 | -102 | 194 | -0.53 |
| **n=250** | 0.86 | 0.91 | -89 | 176 | -0.51 |
| **n=325** | 0.86 | 0.91 | -95 | 185 | -0.51 |

CONCLUSION: Performing fully automated segmentation with U-Net based CNNs, training model sample sizes of up to 50 appear to be sufficient for warranting high sensitivity to cartilage thickness loss. This applies when a model is used that is specific to radiographic disease stage.

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## AUTOMATIC SEGMENTATION OF CT IMAGES OF THE KNEE

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INTRODUCTION: Subchondral bone is a growing area of focus in OA research; yet the specific role of bone in the initiation and progression of OA is largely unknown. Large-scale longitudinal imaging studies (e.g., MOST with >4000 CT scans) have great potential to elucidate the role of bone in OA. Though the large-scale nature of these studies presents data analysis challenges; most notably the time required to segment image structures (e.g., manually segmenting one knee takes ~1-1.5 hours, segmenting 4000 scans would take 1.5 years at 8 hours/day). A potential solution to this challenge is automatic segmentation. Advanced model-based and atlas-based automatic segmentation are possible directions. These approaches perform well with healthy joints; though, they are somewhat prone to error with OA knees due to high subject variability and differences in local features (e.g., osteophytes, attrition[1]). Simpler (yet fast) morphological techniques, combined with prior anatomical knowledge, may offer accurate representations of image structures.

OBJECTIVES: Evaluate agreement between knees segmented using a morphologic-based automatic segmentation technique and a gold-standard manual technique.

METHODS: Fourteen participants were included in the study: 7 were classified as normal; 7 classified as OA as per a KL grading system (KL>2). Knees were imaged using CT (voxel size: 0.625 mm isotropic; voltage: 120 kVp; current-time product: 150mAs; number of slices: ~240; scan time: ~90 s). If a patient reported higher pain in one knee, that one was scanned; otherwise, the scanned knee was randomized. For manual segmentation, the tibia, fibula and femur were segmented from the surrounding soft tissue using commercial image processing software (ANALYZE). To start, a region growing seed was placed in individual bones (threshold defined by the half-maximum height method) followed by manual correction with a stylus and an interactive touch-screen tablet. For the automatic segmentation, the original scans were enhanced by using an exponential transformation function. The bones were segmented by thresholding, applying median filters, and flood-filling the axial slices. Based on the local maxima of total bone pixels in the axial direction, the image was divided into patella-femur and tibia-fibula regions. For the patella-femur region, the initial volume of the patella was found using pixel connectivity, erosion, and iterative thresholding. Using this volume as a seed, a region growing algorithm was used to find the full volume of the patella and separate it from the femur. A similar approach was used to segment the fibula from the tibia. If the femur was not fully separated from the tibia, the gap between them was found by using iterative thresholding. Agreement between the automated and manual segmentation approaches was evaluated using two dice scores, one for the total bone and the other for the bone surface (+/- 1 layer). We report mean and standard deviation (SD) for dice scores from normal and OA knees.

RESULTS: Mean total dice scores ranged from 97.3% to 98.3% for normal knees and 96.8% to 97.7% for OA knees (Table 1). Mean surface dice scores ranged from 94.9% to 95.6% for normal knees and 88.4% to 89.2% for OA knees (Table 1). Manual segmentation took approximately 1.5 hours per scan to perform. The automatic segmentation code took ~16 seconds per scan.

**Table 1:** Summary of Results

| | Total | | | | Surface | | | |
|---|---|---|---|---|---|---|---|---|
| | Tibia | | Femur | | Tibia | | Femur | |
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Normal | 97.3 | 1.28 | 98.3 | 0.55 | 94.9 | 3.28 | 95.6 | 2.53 |
| OA | 96.8 | 1.79 | 97.7 | 1.38 | 88.4 | 5.45 | 89.2 | 8.89 |

CONCLUSION: Our results indicate that this automatic segmentation approach can accurately segment the knee in a rapid manner. This method may prove useful for large-scale longitudinal imaging studies.

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REFERENCES: [1] Liu et al., 2018
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**ENDOGENOUS ANANDAMIDE AND SELF-REPORTED PAIN ARE SIGNIFICANTLY REDUCED AFTER A TWO-WEEK MULTIMODAL TREATMENT WITH AND WITHOUT RADONTHERAPY IN PATIENTS WITH KNEE OSTEOARTHRITIS – A PILOT STUDY**

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INTRODUCTION: Multimodal therapies comprising spa applications are widely used as non-pharmaceutical treatment options for musculoskeletal diseases.

OBJECTIVE: The purpose of this randomized, controlled, open pilot study was to elucidate the involvement of the endocannabinoid system in a multimodal therapy approach in osteoarthritis.

METHODS: 25 elderly patients with knee osteoarthritis received a two-week spa therapy with or without combination of low dose radon therapy in the Bad Gastein radon gallery. A 10-point numerical rating scale (pain in motion and at rest), WOMAC questionnaire and the EuroQol-5D (EQ-5D) questionnaire were recorded at baseline, and during treatment period at week one and two, and at three-month and six-month follow-ups. Plasma levels of the endocannabinoid anadamide (AEA) were determined at baseline and at two-weeks, and serum levels of several cartilage metabolism markers at all five time-points.

RESULTS: A significant and sustained reduction of self-reported knee-pain was observed in the study population, but no further significant effect of the additional radon therapy above base therapy. This pain reduction was accompanied by a significant reduction of AEA plasma levels during treatment in both groups. No significant differences were seen in serum marker concentrations between the groups treated with or without radon, but a small reduction of serum cartilage degradation markers was observed during treatment in both groups.

CONCLUSION: This is the first study investigating AEA levels in the context of a non-pharmacological OA treatment. Since the endocannabinoid system represents a potential target for the development of new therapeutics, further studies will have to elucidate its involvement in OA pain.

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**ADVERSE IMAGING OUTCOMES AFTER INTRA-ARTICULAR CORTICOSTEROID INJECTIONS FOR HIP AND KNEE OSTEOARTHRITIS: AN ILLUSTRATIVE REPORT**

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INTRODUCTION: Injection of intra-articular corticosteroids (IACSs) is a common procedure and usually combined with local anesthetics. It is performed to treat pain related to hip and knee osteoarthritis (OA). However, some concerns over accelerated rates of OA progression have been raised.

OBJECTIVE: To describe and illustrate the imaging findings of possible adverse outcomes following IACS injections in the hip and knee from a single institution.

METHODS: Our institution is a city hospital that provides care for underserved individuals. Many patients have multiple comorbidities that are frequently not well controlled and may be contraindications for surgery; thus, referrals for IACS injections to treat painful hip or knee OA are common. All IACS injections in the hip and knee joints are performed under US guidance by musculoskeletal radiologists. Approximately 500 IACS injections are performed annually for the hip and knee joints combined. We present findings that we observed after IACS injections in patients that had follow-up imaging at our institution (based on non-systematic recall) within a one-year period.

RESULTS: Of 459 injected patients in 2018, 218 did not have X-ray or MRI follow-up or had total joint replacement without additional pre-surgical imaging. We observed 4 possible complications after IACS injections: (a) accelerated OA progression or rapidly progressive osteoarthritis type 1 defined as radiographic joint space loss of more than 2 mm within an approximately 12-month period, (b) subchondral insufficiency fracture on MRI, i.e. fracture line beneath the chondral plate and marked surrounding bone marrow edema pattern that is more intense than would be expected for typical OA, (c) complications of osteonecrosis with pain likely due to the presence of subchondral bone plate collapse on X-ray or MRI, and (d) rapid joint destruction, including bone loss also called rapid progressive osteoarthritis type 2 not typically seen in patients with OA. Altogether, based on the available post-procedural imaging we recorded 36 adverse joint outcomes in 36 patients (19 females) out of 459 IACS injections (8%). These patients were 37-79-year-old (mean of 57 years) and received 1-3 IACS injections (mean 1.4) with 2-15 months between the time of injection and imaging documentation of the joint event (mean of 7 months). Most of the patients (72%) had a pre-procedural Kellgren-Lawrence (KL) knee or hip grade 3 (moderate OA; KL grade 0 = 1; KL grade 2 = 8; KL grade 3 = 26; and KL grade 4 =1) (1).

CONCLUSION: Adverse joint outcomes after intra-articular corticosteroid (IACS) injection, including accelerated osteoarthritis progression, subchondral insufficiency fracture, complications of osteonecrosis, and rapid joint destruction with bone loss, are becoming more recognized by physicians, including radiologists, who may consider adding these risks to the patient consent. Additional systematic research is needed to determine whether these findings were already present at the time of IACS, which patients are at risk and how common these findings are.

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REFERENCE: (1) Kompel AJ, Roemer FW, Murakami AM, Diaz LE, Crema MD, Guermazi A. Intra-articular Corticosteroid Injections in the Hip and Knee: Perhaps Not as Safe as We Thought? Radiology 2019;293:656-663.
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**DOSE-RESPONSE RELATIONSHIP OF AMBULATORY LOAD AND MECHANOSENSITIVE CARTILAGE BIOMARKERS – EXPERIMENTAL FRAMEWORK**

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INTRODUCTION: Blood biomarkers associated with articular cartilage and other joint constituents, as well as cytokines, have been used as surrogate parameters of cartilage metabolism and its degeneration. These markers have been found to be altered in subjects with OA, and temporarily after cyclic exercise. Biomarker concentrations and their longitudinal changes after weight bearing exercise may predict future cartilage degeneration. To date, there is limited evidence for the role of age, sex, injury and tissue status in the dose-response relationship between ambulatory load magnitude and blood marker kinetics.

OBJECTIVE: The current state of research raises the following questions:

1. Is there biological variation in the dose-response relationship between ambulatory load and mechanosensitive cartilage blood markers concentrations, and to which degree can these be explained by age, tissue status or the presence of inflammation?
2. Does the individual dose-response relationship between ambulatory load and mechanosensitive cartilage blood markers predict future cartilage degeneration in persons at risk for developing early OA?

METHODS: In this prospective experimental multimodal study, with block randomization and crossover, we are collecting clinical, biomechanical and biological data of 96 subjects (4 subgroups of n=24: healthy participants aged 20-30 and 40-60 years, and ACL injured participants aged 20-30 and 40-60 years). Participants are examined clinically, undergo gait analysis, and have bilateral MRIs acquired using a clinical IM TSE and custom qDESS sequence (3T MR Prisma, Siemens), at baseline and at 2-year follow-up. Within 1 month after baseline, venous blood samples are collected at three different days immediately before, and up to 210 minutes after 30-minutes of treadmill walking with either 20% reduced, normal or 20% increased bodyweight. Spatiotemporal gait parameters, vertical ground reaction force (vGRF) and sagittal joint kinematics are recorded during treadmill walking. Serum sample concentrations will be measured using ELISAs and normalized to the baseline concentrations. Articular cartilage of weight bearing tibiofemoral regions will be assessed using WORMS, and cartilage thickness and T2 relaxation time by an independent contractor (Chondrometrics GmbH). The different effects on blood biomarker serum kinetics will be estimated using mixed model calculations. We will analyse changes in cartilage thickness and T2 relaxation time from baseline to 2-year follow up, their association with load-induced changes in biomarker concentrations at baseline, as well as differences between age groups and ACL status.

RESULTS: Pilot results (n=24) showed that the load modification framework reduces and increases mean vGRF by -19.5% and +16.8% bodyweight, respectively, with no clinically relevant differences in spatiotemporal parameters and joint kinematics between loading conditions. Moreover, load-dependent changes in blood biomarker kinetics were observed. Test images of qDESS have been obtained and QCd.

CONCLUSION: We consider the combination of repeated MRI, biomechanical analysis, and cartilage serum biomarker analysis after walking with altered ambulatory load as an effective approach to extend current knowledge on serum biomarker metabolism and its association with future cartilage degradation.

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**A MACHINE LEARNING APPROACH TO DISTINGUISH BETWEEN KNEES WITHOUT AND WITH OA USING MRI-BASED RADIOMIC FEATURES FROM TIBIAL BONE**

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INTRODUCTION: Radiomics has been successfully applied to different MRI data, but it has not yet been widely used for assessment of knee OA on MRI. As MRI enables assessment of multiple tissues in a joint, extraction of quantitative imaging biomarkers from bone would be beneficial to get a comprehensive view of the tissue changes associated with OA.

OBJECTIVE: Our aim was to assess the ability of semi-automatically extracted MRI-based radiomic features from tibial bone to distinguish between knees without and with OA.

METHODS: The study data consisted of 665 females from the Rotterdam Study scanned with a 1.5T MRI scanner (Signa Excite 2, GE Healthcare). The mean (SD) age and body mass index of the subjects were 54.6 (3.7) years and 26.8 (4.6) $kg/m^2$, respectively. A fast imaging employing steady-state acquisition (FIESTA) sequence (repetition time: 5.7, time to echo: 1.7, flip angle: 35 degrees, voxel size: 0.3 x 0.3 x 0.6 $mm^3$) was used in the quantitative analyses. The Medical Ethics Committee of Erasmus University Medical Center approved the study and all subjects provided written consent. Tibial bone from the right knees of the participants was segmented using an automatic segmentation method that combines multi-atlas and appearance models. Twenty manually segmented tibias were used to train the segmentation method. The segmentation performance was evaluated on five manually segmented tibias. Altogether six 3-D volumes of interest (VOIs) were semi-automatically extracted from the medial and lateral compartments of the tibia. Radiomic features that are related to the shape and texture of the region, were calculated from each VOI using an open-source Workflow for Optimal Radiomics Classification package in Python. Features associated to the shape were calculated only for the whole tibial volume. MRIs were scored according to the semi-quantitative MRI OA knee score (MOAKS). Tibiofemoral OA was defined as the presence of a full thickness cartilage loss and definite osteophyte, or one of the abovementioned features and two of the following features: partial-thickness cartilage loss, subchondral bone marrow lesion or cyst, or meniscal subluxation, maceration or degeneration. Elastic Net, which is a regularized logistic regression method, was used for classification. We used 10-fold cross-validation with 100 repeats to train the models. Performance of the covariate (age and body mass index) model, radiomic features model, and combined covariate + radiomic features model to distinguish between knees without and with OA were assessed using an area under the receiver operating characteristics curve (ROC AUC). Statistical analyses and elastic net experiments were done using R software (version 3.5.2).

RESULTS: Of 665 analyzed knees, 76 (11.4%) had tibiofemoral OA. The mean Dice similarity coefficient for the automatic segmentation of the tibia was 0.96 (SD: 0.02) An ROC AUC value of 0.68 (95% confidence interval (CI): 0.60–0.75) was obtained to distinguish between knees without and with OA using the covariate model. Image features model yielded an ROC AUC of 0.80 (CI: 0.73–0.87). The model that combined image features from all VOIs and covariates had an ROC AUC of 0.80 (CI: 0.73–0.87).

CONCLUSION: The image features model had higher ROC AUC than covariate model to distinguish between knees without and with osteoarthritis. Our results suggest that radiomic features are useful imaging biomarkers of bone. An advantage of assessing bone on MRI instead of on radiography is that other tissues involved in OA can be assessed simultaneously.

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**NOVEL MICROCOMPUTED X-RAY TOMOGRAPHY METHOD FOR ANALYZING CARTILAGE CHANGES IN RAT PARTIAL MENISCECTOMY MODEL**

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INTRODUCTION: Imaging biomarkers are widely used in pre-clinical OA studies to provide structural and compositional indicators of disease severity and treatment efficacy.

OBJECTIVE: To establish a quantitative, contrast-enhanced micro-computed tomography (CEμCT) -based technique for articular cartilage (AC) degeneration assessment, with similar sensitivity to quantitative magnetic resonance imaging (MRI) but superior spatial information.

METHODS: Partial medial meniscectomy (pMMx) surgery was performed in the right knees of skeletally mature male Lewis rats (*N*=10), while the contralateral knees served as controls. MRI was performed for both knees at 3- and 5-weeks post-surgery (*N*=5). T2 relaxation time was evaluated using a multi-slice spin-echo sequence with a slice thickness of 0.5 mm and field strength of 7 T. Following MRI, rats were euthanized, and knees dissected and fixed in neutral-buffered formalin. The legs were stained with 3% phosphotungstic acid (PTA) for 16 h and imaged with μCT (voxel size: 6μm). A novel analysis method was used to evaluate (AC) thickness and surface degeneration. Thickness was analyzed with a sphere fitting technique on segmented cartilage volumes. The surface degeneration was analyzed by fitting a polynomial reference surface (RS) 30μm on top a smoothed surface and calculating the local distances between the RS and the original surface. Distances more than 50μm were classified as degenerated. Differences between the groups were determined using a linear mixed model.

RESULTS: There was a significant increase in T2 relaxation time between control and pMMx on the medial side (Fig. 1A). AC thickness was greater in the control legs at 3 weeks as compared to 5 weeks. The AC was thicker on the medial and lateral tibia when comparing pMMx and control knees at the 5-week time point. AC degeneration was evident in the medial tibia of the pMMx-knee, where degeneration of 18.6% and 24.5% was observed at the 3- and 5-week time points, respectively.

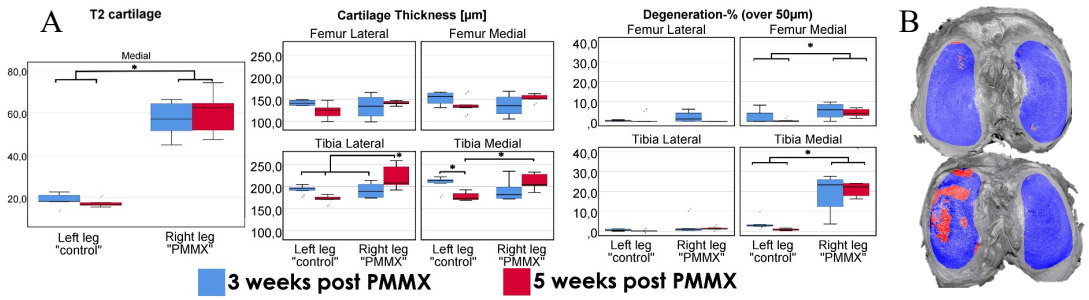


**Figure 1.** A) Boxplots from T2, cartilage thickness and degeneration %. A star indicates statistical significance between groups. B) Example images from a control tibia (top) and a pMMx tibia (bottom) where red areas are classified as degenerated and blue areas as not degenerated.

CONCLUSION: The CEμCT allowed for a detailed analysis of AC degeneration. The results indicate that the thickness of AC increases on the operated knee from 3- to 5-weeks despite the surface degeneration on the medial side. High resolution imaging of full joint with CEμCT allows quantitative analysis of cartilage morphology and erosion. Compared to MRI, CEμCT provides a more detailed picture of OA associated cartilage changes from swelling to surface degeneration. (Fig. 1B) This CEμCT technique could be used when evaluating pharmacotherapeutic options in pre-clinical animal models.

SPONSOR: none
DISCLOSURE STATEMENT: none
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**APPLICATIONS OF CARTILAGE IMAGING AND SERUM BIOMARKERS TO SPACE FLIGHT**

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INTRODUCTION: Conditions of the musculoskeletal system depend on its exposure to mechanical loads. Living in microgravity - an environment that provides the most radical model of mechanical unloading - immediately leads to catabolic adaptation of muscle and bone tissue. To date, the understanding of the effects of the microgravity environment on articular cartilage is insufficient. While it is known that healthy articular cartilage relies on adequate mechanical loading, the effects of immobilization of healthy tissue, independent of injury or disease, are not well understood. Immobilization as a result of injury has been shown to lead to loss of cartilage thickness in the knee joint and to altered mechanical properties of cartilage tissue.

OBJECTIVE: The aim of the 'Cartilage' experiment was to investigate the effect of immobilization on cartilage health hypothesizing that unloading the skeleton of healthy individuals during a 4 – 6 months stay on the international space station will negatively affect cartilage health.

METHODS: 12 astronauts of the USOS (United States orbital segment) ISS crew with a mission length of 4 to 6 months participated in the study. MRI of the knee joint was performed before launch ((L) -60 days) and after return to Earth (Return (R)+7, R+28, R+365 days). Blood and urine samples were collected at the time of MRI data collection, and additionally on R+1. From a 3D DESS sequence, regional cartilage thickness of the weight-bearing femur, tibia and patella was quantified using Chondrometrics 3.0 software (Ainring, Germany). Serum concentrations of COMP, C2C, CPII, CS-846 were analyzed using commercial ELISA (enzyme-linked immunosorbent assays) kits.

RESULTS: Preliminary analysis of cartilage thickness from MRI suggests that sub-regional changes occurred at the medial tibia (external: +3.1% ($\alpha<0.05$), posterior: +3.0% ($\alpha<0.05$, N=12). Preliminary serum biomarker analysis shows an increase in resting serum levels compared to pre-flight concentrations for C2C, CPII and CS-846 at R+1, R+7 and R+30 and for C1,2C at R+1 and R+7. While there was no difference in resting serum COMP concentration between L-60 und R+1, levels increased within the first week of return (R+1 vs. R+7: + 20.7%, $p<0.05$) and did not recover within the first month after return (R+30: + 24.0%, $p<0.05$). Noticeable are the pronounced inter-individual differences in the response of cartilage thickness and serum biomarkers that are apparent from the different crewmembers.

CONCLUSION: This is the first study to investigate the effects of microgravity on articular cartilage in healthy astronauts. Cartilage tissue appears to be sensitive to a prolonged stay in microgravity, as suggested by changes in cartilage thickness and serum biomarkers. These results confirm that a reduction of mechanical load can potentially initiate catabolic adaptation of the cartilage tissue, which may increase the risk of joint injury during or after long-term space flight. The pronounced inter-individual differences emphasize the importance of identifying risk factors that enhance degenerative processes in cartilage tissue during long-term missions. Further, space flight offers a unique model for the investigation of the tissue response to a reduction of mechanical loading in healthy subjects.

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**HYBRID PET-MRI REVEALS THE ASSOCIATION BETWEEN OSTEOPHYTE METABOLIC ACTIVITY AND ADJACENT SYNOVITIS**

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INTRODUCTION: Evidence from in-vitro and animal studies suggests that synovitis plays a role in osteophyte (OP) development and progression in OA via effects on the adjacent bone and periosteum. Evidence of this phenomenon in humans would improve understanding of OA development and support the targeting of synovial inflammation to achieve disease modification.

OBJECTIVES: Assess the association between OP metabolic activity and intensity of adjacent synovitis using hybrid [$^{18}$F] sodium fluoride ([$^{18}$F]NaF) PET-MRI.

METHODS: Eleven participants/22 knees were included (age 54 ±12 years, body mass index 26.6 ±3.9 kg/m$^2$, 7 female). Participants had a clinical diagnosis of OA in at least one knee. We performed simultaneous bilateral knee 3T PET-MR imaging (GE Signa PET-MR, GE Healthcare, Waukesha, WI) at a single timepoint using bilateral 16 channel flexible receive-only coils (Neocoil, Pewaukee, WI). PET imaging was performed following the administration of 2.5 mCi [$^{18}$F]NaF. OP metabolic activity was quantified using standardized uptake values ($SUV_{mean}$ and $SUV_{max}$) and the kinetic parameters $K_1$ (bone perfusion), $K_i$ (rate of clearance of [$^{18}$F]NaF from the blood plasma to the bone mineral compartment) and extraction fraction (the fraction of [$^{18}$F]NaF entering bone tissue that binds to bone matrix as opposed to being cleared back into the plasma pool) derived from Hawkins compartmental modelling of dynamic data. MR was performed simultaneously with PET acquisition and included matching pre and post contrast 3D fat-suppressed SPGR sequences for synovial segmentation and dynamic contrast-enhanced (DCE) sequences. Synovitis was quantified using $K^{trans}$, the volume transfer coefficient between the blood plasma and the extracellular extravascular space, derived from extended Tofts compartmental modelling of DCE-MRI data. Bone and synovium were segmented automatically. Osteophyte grading was performed according to the MOAKS system by a board-certified musculoskeletal radiologist. The relationship between PET parameters of OP metabolism and adjacent $K^{trans}$ was assessed via Spearman correlation coefficients and mixed-effects linear regression analysis adjusting for within knee and within participant clustering.

RESULTS: A total of 88 OPs were detected in 22 knees (54 x MOAKS grade 1 – small, 29 x grade 2 – medium, 5 x grade 3 – large). Modest positive correlations were observed between OP $SUV_{mean}$ (r = 0.71), $SUV_{max}$ (r = 0.64), $K_1$ (r = 0.68) and $K_i$ (r = 0.64) and adjacent synovial $K^{trans}$, whereas a weak negative correlation (r = -0.34) was observed for extraction fraction (all correlations were significant at $p < 0.001$). After adjusting for within knee and within participant clustering, all OP PET parameters were significantly ($p < 0.05$) and positively associated with adjacent synovial $K^{trans}$ with the exception of extraction fraction. $SUV_{mean}$ had the strongest association; in the fitted model, for every SD increase in $SUV_{mean}$, $K^{trans}$ increases by 0.028 min$^{-1}$ (95% CI 0.011, 0.044), approximately 70% of the median whole joint value.

CONCLUSION: There is a positive association between OP metabolic activity and intensity of adjacent synovitis. The association appears to be primarily driven by increased OP perfusion.

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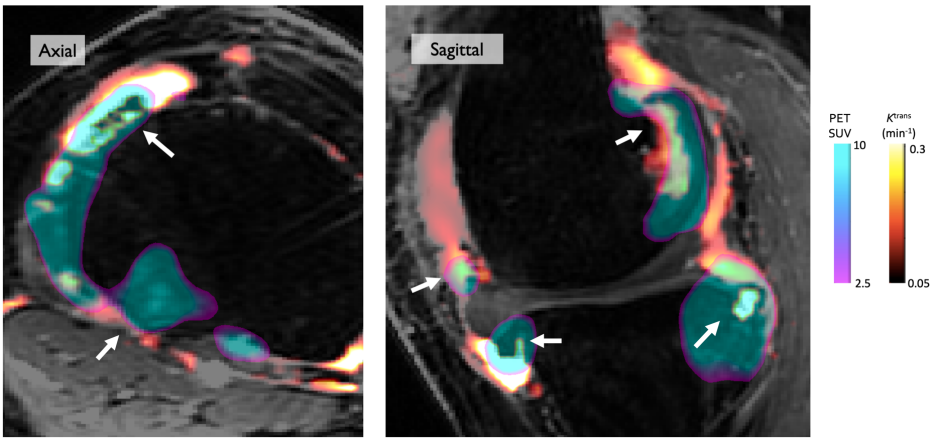


Representative axial and sagittal post-contrast 3D SPGR FS MR images overlaid with DCE ($K^{trans}$) and PET (SUV) data. Note increased [$^{18}$F]NaF uptake within multiple osteophytes (white arrows) with adjacent high $K^{trans}$ values.

**SAMPLE SIZE FOR EXPERIMENTAL MEDICINE STUDY DESIGNS IN KNEE OA USING QUANTITATIVE IMAGING BIOMARKERS OF SYNOVITIS**

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INTRODUCTION: Experimental medicine studies involve the use of innovative measurements (including quantitative imaging biomarkers, QIBs) in human subjects to establish early proof-of-concept (POC) of new treatments. However, the use of experimental medicine study designs incorporating QIBs in OA is limited, likely due to the belief that significant changes will not be detectable given the short follow-up periods (typically ≤ 6 months) and small participant numbers involved.

OBJECTIVES: Establish the sample size required to demonstrate a reduction of 50% of the difference between mean OA and mean age-matched healthy reference values ($\Delta_{50}$, a plausible effect size based on prior data) for three different synovitis QIBs in a putative experimental medicine study of knee OA.

METHODS: Sample size calculations are based on pilot data from a prospective observational study of 15 knee OA (KL 2/3, medial compartment predominant disease, 40-60 years old) and 6 age-matched healthy control (HC) participants. Knee MR imaging was performed at baseline and 6 months on a 3T platform (GE 750) using an 8-channel transmit/receive knee coil (Invivo). MR pulse sequences included matching pre and post contrast 3D fat-suppressed SPGR sequences for synovial segmentation and dynamic contrast-enhanced (DCE) sequences for pharmacokinetic assessment of synovitis.
We derived three QIBs from the imaging data to assess different aspects of synovitis: synovial volume as a measure of extent of synovitis, and the initial area under the time-gadolinium concentration curve at 60s ($IAUC_{60}$) and the volume transfer coefficient between the blood plasma and the extracellular extravascular space ($K^{trans}$) as quantitative measures of intensity of synovitis. We calculated these QIBs using both manual and semi-automatic synovial segmentation approaches. We determined $\Delta_{50}$ using baseline OA and HC data. The standard deviation of 6-month change was calculated for each QIB with bootstrap estimation of 95% confidence intervals. Correlation between baseline and 6-month values was also estimated. These data were used to perform sample size calculation for a putative experimental medicine study comparing active treatment vs placebo (2 equal groups) assuming a repeated measures design with 80% power to detect a difference between groups of $\Delta_{50}$ and a tolerable type 1 error rate of 5%.

RESULTS: Results are summarized in table 1. Reduced sample size estimates are seen for intensive/functional vs extensive/morphological QIBs. This is a result of reduced (relative) standard deviation of 6-month change and improved differentiation between OA and HC participants. For $IAUC_{60}$ and $K^{trans}$, semiautomatic segmentation of the synovium reduces required sample size but not for synovial volume.

CONCLUSION: This work demonstrates the potential utility of QIBs of synovitis to establish early POC for synovitis-targeted therapies in experimental medicine studies. The effect sizes used here are feasible based on prior studies of intra-articular steroid administration in knee OA. Reduced sample size estimates for intensive vs extensive QIBs suggests that full DCE-MRI acquisition is worth the additional effort. A key limitation is that the pilot data used for sample size calculation come from a small single center study, however we have used bootstrapping to mitigate the risk of deriving over-optimistic estimates.

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| QIB | Sample size per group (95% CI) | |
|---|---|---|
| | Manual segmentation | Semiauto segmentation |
| Synovial volume | 54 (13, 65) | 273 (108, 540) |
| $IAUC_{60}$ | 43 (21, 72) | 24 (12, 38) |
| $K^{trans}$ | 30 (14, 59) | 24 (18, 44) |

**Table 1**: Sample size estimates for synovitis QIBs

**DIAGNOSTIC PERFORMANCE OF REGION- AND LAYER-SPECIFIC CARTILAGE TRANSVERSE RELAXTION TIME (T2) IN PRE-RADIOGRAPHIC AND RADIOGRAPHIC KNEE OSTEOARTHRITIS - DATA FROM THE OSTEOARTHRITIS INITIATIVE**

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INTRODUCTION: MRI transverse relaxation time (T2) has been proposed as an imaging biomarker for detecting OA-related alterations in articular cartilage composition before the onset of radiographic knee OA. A recent meta-analysis reported cartilage T2 to significantly discriminate OA vs. controls, but these analyses did not demonstrate diagnostic sensitivity across pre-radiographic stages of early OA where T2 is thought to be most effective as an "early OA" marker.

OBJECTIVE: To test the diagnostic performance of laminar articular cartilage T2 across different strata of knee OA in a cross-sectional study, with a particular focus on pre-radiographic stages. In addition, we tested the hypothesis that cartilage T2 change starts in the superficial layer of central femorotibial subregions, and that ratios of central superficial vs. central deep T2 as well as central vs. peripheral superficial or deep T2 may enhance diagnostic performance.

METHODS: Cartilage T2 was measured at year-1 follow-up MESE images of 400 right knees of Osteoarthritis Initiative (OAI) participants. The sample included a) 88 knees from the healthy reference cohort (bilateral Kellgren & Lawrence grade [KLG] 0, no pain and no risk factors for OA), b) 74 KLG0 knees from participants that were contra-laterally KLG0 but had general OA risk factors, c) 26 KLG0 knees with contra-lateral osteophytes, d) 41 KLG0 knees with contra-lateral radiographic joint space narrowing (JSN), e) 76 KLG1 knees, f) 14 KLG2 knees without JSN, and g) 81 KLG 2/3 knees with JSN. Superficial and deep T2 were calculated from manual segmentations in the medial (MFTC) and lateral compartment (LFTC). Central (cMFTC/cLFTC) and peripheral (perMFTC/perLFTC) T2 values were calculated. Statistical comparisons were performed by analysis of covariance, with adjustment for age, sex, and BMI for 1) comparing laminar cartilage T2 between all groups, 2) comparing T2 between pre-radiographic stages (groups a- d). Partial $\eta^2$ was used as measure of effect size.

RESULTS: Superficial cMFTC T2 tended to increase with greater radiographic involvement from healthy to KLG1, but T2 in those with definite ROA was similar to that observed for group c or d. Between-group differences (across all stages) were statistically significant for cMFTC, perMFTC and perLFTC, but not for cLFTC. When limiting the analysis to pre-radiographic stages (groups a-d), statistically significant differences were observed for peripheral (medial and lateral) but not for the central regions. Deep layer T2 also tended to increase with greater radiographic involvement. As for the superficial layer, between-group differences (all stages) were statistically significant for cMFTC, perMFTC , and cLFTC but not for perLFTC. However, no statistically significant differences were observed when limiting the analysis to the pre-radiographic stages. The superficial:deep layer ratio ranged from 1.37±0.13 (group f) to 1.49±0.18 (group e) for cMFTC and from 1.36±0.15 (group g) to 1.44±0.12 (group e) for cLFTC. The between-group differences (across all stages) attained statistical significance ($p<0.01$). The effect sizes were, however, comparable to those observed for superficial and deep layer T2; no statistically significant differences were observed across pre-radiographic stages. The central:peripheral T2 ratio showed only little variation between groups.

CONCLUSION: Between group differences were captured by both superficial and deep layer cartilage T2, and in central as well as peripheral subregions. Yet, the hypothesis that central subregions provide better discrimination across radiographic (or pre-radiographic) strata was refuted, with peripheral superficial subregions more efficiently differentiating pre-radiographic stages. The ratio between the superficial vs. deep layer or the central and peripheral T2 did not enhance the diagnostic performance. Superficial layer T2 hence is a promising diagnostic marker and should include peripheral subregions.

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**WHERE ARE THE NEW CLINICAL TRIALS IN OSTEOARTHRITIS? A REVIEW OF CLINICLATRIALS.GOV AND TRIAL FINDER IMAGING**

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INTRODUCTION: Osteoarthritis is a crippling disease that affects 32.5 million US adults (CDC.gov, 2020) and at least 15% of adults older than 60 globally (Arthritis.org, 2019) and yet there are still no disease modifying anti-osteoarthritis drugs (DMOADs) available for treatment or prevention. It would be anticipated that with such a prevalent disease with high impact on individual quality of life, there would be extensive research and clinical trials being undertaken.

OBJECTIVE: To evaluate the clinical trial landscape to identify the number of new trials in osteoarthritis, both in general and those employing medical imaging.

METHOD: All clinical trials in the USA and generally worldwide are registered on www.clinicaltrials.gov (CT.gov) Although this does not cover 100% of the global trials, any trial wishing to be published in a medical journal will need a National Clinical Trial (NCT) number, so this database will provide a significant insight into the number of trials globally being conducted and certainly all trials in the USA. A search in CT.gov was conducted using the search criteria "Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Interventional Studies | Osteoarthritis | Industry | Start date from 01/01/2015 to 06/30/2020". Also, TrialFinder Imaging dataset was interrogated (Bracken Data Inc) for the same dates and search criteria. This dataset uniquely provides those trials with medical imaging terminology (using a natural language processor) in the protocol either in the title, eligibility criteria or in the main body of the information on CT.gov.

RESULTS: From CT.gov 408 studies were identified in the last 5 years that included osteoarthritis. When the search criteria were limited to industry sponsored and active (recruiting or non-recruiting) the number was reduced to 191 studies. When the data was further detailed to those studies with medical imaging outcomes (TrialFinder Imaging) a total of 28 clinical trials were identified by 23 sponsors. The phases 1, 2 and 3 had 9, 10 and 9 trials respectively. 14 of the 28 trials used MRI. 3 of the studies were evaluating anti-NGF's. 6 new trials were started in 2020. The country with the highest number of imaging studies was USA (11 studies). As a comparison if CT.gov was used and the outcome of "imaging" was put in the search, only 18 studies were identified.

CONCLUSION: There is a lack of clinical trials and development in the field of osteoarthritis. The lack of trials utilizing medical imaging provides insight into the minimal development of DMOADs by the pharmaceutical industry. The challenge of finding a DMOAD treatment has been frustrated with failures. With this current dearth of clinical trials there is need to carefully evaluate the earlier failures to ensure that medical and regulatory agencies can more closely collaborate to support the development of new therapeutic interventions to reduce the global disease burden of osteoarthritis.

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**OPEN MRI VALIDATION OF A HIP MODEL PREDICTING FEMOROACETABULAR IMPINGEMENT USING MOTION CAPTURE DATA**

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INTRODUCTION: Today, most cases of hip OA which were previously considered as idiopathic, are attributed to cam and pincer morphologies, subtle bony abnormalities of the femoral head-neck junction and acetabular rim. Cam and pincer morphologies (CPM) are also a common finding in young and middle-aged populations with hip pain. However, not all hips with CPM will develop OA or become painful. Anterior impingement between the femoral head-neck junction and acetabular rim during motion and in extreme hip angles is a proposed pathomechanism in CPM hips. Understanding how activity and deformity combine to produce impingement may shed light on the causes of OA and pain in CPM hips.

OBJECTIVE: Determine the accuracy of a subject-specific hip model driven by subject-specific motion data at predicting femoroacetabular impingement (FAI) during squatting and sitting flexion, adduction, and internal rotation (FADIR) - two maneuvers (active and passive) with extreme hip angles proposed to provoke impingement.

METHODS: We recruited 33 participants including 9 with cam and/or pincer morphology and hip pain (CPM+), 13 with cam and/or pincer morphology and without hip pain (CPM-), and 11 controls from the Investigations of Mobility, Physical Activity, and Knowledge Translation in Hip Pain (IMPAKT-HIP) cohort. We developed 3D subject-specific hip models from each participant's study hip scan in supine using a sequence optimized for hip cortical bone visualization in a 3T MRI scanner (Achieva, Philips, Eindhoven, Netherlands). We collected 3D kinematic data of each participant during squatting and sitting FADIR maneuvers at 120 Hertz (Hz) using a fourteen-camera motion capture system (Motion Analysis Corporation, Santa Rosa, CA). To measure impingement directly and to define a hip joint coordinate system and calculate hip joint angles, we scanned each participant's pelvis, study hip and knee in supine, as well as study hip in standing, squatting and sitting FADIR poses with an upright open MRI scanner (MROpen, Paramed, Genoa, Italy). To measure impingement in squatting and sitting FADIR directly, we acquired scans in planes parallel to the femoral neck and perpendicular to the femoral neck and femoral shaft axes (alpha angle plane). We calculated hip joint angles during squatting and sitting FADIR maneuvers from motion data and at squatting and sitting FADIR postures scanned at the MROpen through registration of supine scans to posture scans. Impingement was quantified through the beta angle, which defines clearance between the femoral head/neck and acetabular rim and was measured on the alpha angle plane. Hip position for the squatting and sitting FADIR postures imaged in the MROpen scanner was matched to the motion analysis data by choosing the frame of motion analysis data that yielded the minimum least square error between hip joint angles in the MROpen and motion analysis data. Hip 3D models segmented from the 3T scans were positioned to this identified time frame. We calculated the beta angle from the positioned model and compared it to direct measurements of the beta angle made using MROpen scans of the hips in the same postures. Only participants that yielded least square error of mean joint angles below 1 percent and 3 percent, for sitting FADIR and squat respectively, were included in final accuracy calculation. The threshold for squat and sitting FADIR were defined through assessment of relation between least square error in joint angles and model accuracy.

RESULTS: For squatting, the mean absolute error (±SD) and root mean squared error (RMSE) between the model prediction of beta angle and the direct measure of beta angle from the MROpen were 1.08° (±0.82°) and 1.33°, respectively. For sitting FADIR, the mean absolute error (±SD) and RMSE between the model prediction of beta angle and the direct measure of beta angle from the MROpen was 0.48° (±0.29°) and 0.55°, respectively.

CONCLUSION: We conclude that this subject-specific hip model driven by subject-specific motion data predicts beta angle (femoroacetabular clearance) with an accuracy of about 1°, which makes it useful to predict impingement during activities measured with motion analysis.

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**QUANTITATIVE MAGNETIZATION TRANSFER MRI AND BIOCHEMICAL CONTENT OF HUMAN CADAVER MENISCI**

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INTRODUCTION: Quantitative magnetization transfer (qMT) MRI is a unique technique in that it assesses free pool (water) and restricted pool (macromolecules such as proteoglycan and collagen) properties of tissues. Previous studies in cartilage have shown moderate correlations between qMT parameters and the biochemical properties[1] and differences between OA patients and healthy individuals[2]; but only proof of concept in cadavers has been shown in the meniscus[3].

OBJECTIVE: To investigate the qMT parameters f (bound pool fraction), $k_f$ (magnetization exchange rate), $T_{1b}$ ($T_1$ relaxation time of the bound pool), $T_{2b}$ ($T_2$ relaxation time of the bound pool), and $T_{1f}$ ($T_1$ relaxation time of the free pool) of human cadaver menisci and identify correlations with proteoglycan and collagen content.

METHODS: Six cadaver knees with no history of knee injury or surgery (3 male and 3 female, mean age 70.3 ± 9.3) were scanned at a 3.0T MR system (MAGNETOM Skyra, Siemens, Erlangen, Germany) using an in-house qMT sequence. The protocol included 10 MT scans (five offset frequencies: 433, 1087, 2732, 6862, 17235 Hz, at two flip angles:142˚ and 426˚) and one gradient echo scan with FOV = 160 x 160 $mm^2$, TR/TE = 48/3 ms, a 256 x 256 matrix, and 0.625 x 0.625 in plane resolution. $B_1$ and $T_1$ maps were also acquired for qMT two-pool modelling. qMT parameters were estimated using a custom fitting/analysis pipeline. After scanning, menisci were dissected, and a 4 mm biopsy punch was used to acquire samples for biochemical analysis. Samples were weighed, vacuum dried, and weighed to determine liquid content and then digested using proteinase K. Proteoglycan and collagen content were assessed using a dimethylmethylene blue (DMMB) assay (using sulfated GAG as a surrogate) and a hydroxyproline assay kit (Sigma Aldrich, MAK008), respectively. qMT and biochemistry data were registered using a custom image processing pipeline and relationships were identified using a Spearman's $\rho$ correlation test (SPSS, Chicago, IL, USA).

RESULTS: Mean qMT parameters (N=60 samples) and biochemical content (N=56 samples) were within the expected range (Table 1). Correlations were carried out on the 56 samples that had qMT, sulfated GAG, and collagen data. Correlations of $\rho = 0.27$, $\rho = 0.29$, and $\rho = -0.27$ all with $p < 0.05$ were found between the collagen per wet mass and $T_{1f}$ relaxation time, $T_{2f}$ relaxation time (Figure 1), and $k_f$ respectively. A correlation of $\rho = 0.27,\ p < 0.05$ was also found between liquid content vs $T_{1f}$ relaxation time.

| Parameter | Mean (SD) |
|---|---|
| $T_{1f}$ (ms) | 597 (104) |
| $T_{2f}$ (ms) | 5.70 (2.47) |
| $T_{2b}$ (μs) | 16.1 (1.47) |
| f (%) | 23.6 (4.29) |
| $k_f$ (1/s) | 3.03 (1.18) |
| sGAG/WM (%) | 0.570 (0.242) |
| Collagen/WM (%) | 25.6 (5.84) |

**Table 1:** Average qMT parameters (N=60) and biochemical content (N=56) for human cadaver menisci. WM is wet mass.

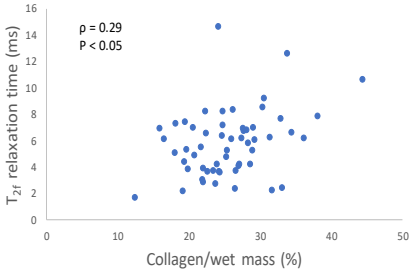


**Figure 1:** Correlation between collagen content per wet mass of menisci and $T_{2f}$ relaxation time (N=56)

CONCLUSION: Average values for qMT parameters align with previous results in the meniscus[3], except for $T_{2b}$ relaxation time in which our values were higher. This is likely due to differences in the fitting algorithm; we used a Gaussian absorption lineshape whereas the other study used a Super Lorentzian lineshape. Weak correlations were found between liquid content and $T_{1f}$ relaxation time as well as three of the five qMT parameters studied and the collagen content. The cadaver specimens were relatively homogeneous, and this may be why stronger correlations were not observed. Future studies of younger and diseased tissues will elucidate potential relationships between qMT parameters and biochemical content in the meniscus.

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**RELIABILITY AND CONCURRENT VALIDATION OF THREE-DIMENSIONAL ULTRASOUND FOR QUANTIFYING KNEE CARTILAGE VOLUME**

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INTRODUCTION: Conventional x-ray radiography and MRI are widely used imaging modalities to clinically assess knee OA, including to monitor changes in femoral articular cartilage (FAC) over time. Radiography only affords indirect assessments of FAC degradation in the form of JSN with poor sensitivity to change. MRI is associated with high operating and manufacturing costs, long wait lists, long scan times, and is inaccessible to many patients, especially in rural communities and developing countries. Objective, imaging-based, point-of-care tools that can feasibly assess OA status, progression, and response to treatment are needed. We have developed a hand-held mechanical three-dimensional (3D) ultrasound (US) device for quantifying FAC volume at the patient's bedside.

OBJECTIVE: Our goal was to test the reliability and validity of a handheld mechanical 3D US device for quantifying FAC volume against the current clinical standard of MRI in healthy knees. We hypothesized that FAC segmentation volumes using 3D US would demonstrate excellent reliability (ICC > 0.90) and be strongly correlated ($\rho > 0.80$) with MRI FAC volumes in the same region-of-interest (ROI).

METHODS: Bilateral knee images of healthy volunteers (n = 25) were acquired using a 3.0 Tesla MRI GE Healthcare scanner and 3D US images were acquired using a Canon Aplio i800 US machine. MR images were acquired using a 3D Multiple Echo Recombined Gradient Echo (MERGE) sequence with an HD T/R Knee Array Coil (8 channels). The excitation flip angle was 5° with a repetition time (TR) of 30 ms and an echo time (TE) of 11.71 ms. 3D US images were acquired using a 14L5 linear transducer with a 58 mm footprint length and an operating frequency of 10 MHz (3.8 MHz – 10 MHz), which was housed in the 3D scanning mechanism. The trochlear FAC was manually segmented from MRI and 3D US by 2 raters who conducted repeated segmentations during an additional session separated by a 2-week washout period. MRI and 3D US segmentations were registered using a semi-automated surface-based registration algorithm, and MRI segmentations were trimmed to match the FAC ROI of 3D US. Intra- (n = 5) and inter-rater (n = 25) reliabilities were assessed using ICC values calculated from FAC volumes. Relationships between MRI and 3D US segmentation volumes were assessed using Spearman Rank-Order correlation and linear regression (n = 25).

RESULTS: MRI intra-rater ICCs were 0.97 [(0.79, 1.00), $p = 0.001$] and 0.90 [(0.25, 0.99), $p = 0.002$] for each rater with an inter-rater ICC of 0.83 [(0.48, 0.94), $p < 0.0001$]. 3D US intra-rater ICCs were 1.00 [(0.98, 1.00), $p < 0.0001$] and 0.98 [(0.84, 1.00), $p = 0.0003$] for each rater with an inter-rater ICC of 0.96 [(0.90, 0.98), $p < 0.0001$]. Spearman Rank-Order correlation and linear regression revealed a strong correlation with $\rho = 0.88$ [(0.75, 0.95), $p < 0.0001$] and regression with $R^2 = 0.85$ [(0.75, 0.95), $p < 0.0001$].

CONCLUSION: We have developed and validated a 3D US device that enables accurate and precise volume measurements of FAC in healthy subjects. 3D US can be used to assess FAC with excellent reliability in healthy knees and therefore warrants further development. Future work will include validation in OA patients and monitoring FAC volume changes over time for future use of 3D US in OA clinical trials and patient care.

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**ULTRASOUND FEATURES OF SYNOVITIS ARE ASSOCIATED WITH KNEE OSTEOARTHRITIS PAIN PATTERNS**

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INTRODUCTION: Knee synovitis measured on MRI is associated with progression of joint damage and pain severity in patients with knee OA (Hill *et al.,* 2007). Synovitis may be a key therapeutic target; however, the experience of OA pain is diverse. Pain presentation may vary based on location, intensity, and frequency, suggesting different pathophysiological mechanisms (Hawker *et al*., 2008; Moreton *et al.,* 2012). Compared with MRI, musculoskeletal ultrasound (MSK-US) is a less expensive and higher resolution imaging method to assess synovitis in clinical and research settings. US may assist our understanding of the relationship between synovitis and OA pain patterns and may help to inform treatment algorithms.

OBJECTIVES: The aims of this study were to test the association of US-based measures of synovitis with patient-reported outcome measures of pain, and with intermittent and constant pain patterns.

METHODS: We analyzed cross-sectional baseline data of patients with knee OA from the Western Ontario Registry for Early Osteoarthritis Knee Study (WOREO). All individuals over age 18 with a clinical diagnosis of symptomatic knee OA were invited to participate. Self-reported pain symptoms were measured using the validated Knee Injury and Osteoarthritis Outcome Score Pain subscale (KOOS Pain; 0-100; lower scores indicate more pain) and the Intermittent and Constant Osteoarthritis Pain (ICOAP; 0-100; higher scores indicate more pain) instruments. Further, ICOAP Pain phenotypes were defined as None, Intermittent Pain only, Constant Pain only, and Both Intermittent and Constant (Carlesso *et al.,* 2020). MSK-US was used to measure synovitis (0-3; None-Severe) and presence of synovial Power Doppler (PD) signal (0/1; absent/present) in the suprapatellar region of the knee. Radiographic Kellgren-Lawrence (KL) grades were used to define Early (Grade ≤ 2) or Late (Grade ≥ 3) stage knee OA. We fitted a series of multivariate linear and multinomial logistic regression models to evaluate the association between US-synovitis (predictor) and pain (outcome), adjusting for age, sex, BMI, PD, and KL grade. Linear model outcomes were 1) KOOS Pain Subscale, 2) ICOAP Constant Pain, and 3) Intermittent Pain. We reported results as unstandardized beta coefficients with 95% confidence intervals (CIs) with robust standard errors. Multinomial logistic model outcome was 4) ICOAP Pain phenotypes. We reported results as relative risk ratios (RRR) with 95% CIs with robust standard errors.

RESULTS: Analyses included 183 patients. Model 1 indicates that Mild and Severe synovitis were associated with lower scores on the KOOS Pain subscale (higher pain) vs. No synovitis (-7.35 [-14.29 to -0.40] and -19.92 [-31.03 to -8.82], respectively). Consistent with this finding, late stage OA was associated with lower KOOS scores vs. early stage OA (-9.11 [-15.20 to -3.03]). Interestingly, Model 2 suggested higher levels of synovitis might be associated with lower ICOAP Intermittent pain scores (less intermittent pain), although wide confidence intervals around these beta estimates precluded statistical significance. Model 3 demonstrated Severe synovitis was associated with higher ICOAP Constant pain subscale scores (23.80 [2.62 to 44.98]). Similarly, late stage OA was also associated with higher Constant pain scores vs. early stage OA (10.73 [0.02 to 21.44]). In the multinomial regression model, patients with Moderate and Severe synovitis had 7.04-fold [1.02 to 62.78] and 51.97-fold [4.49 to 625.66] increases, respectively, in risk of reporting Constant Pain only vs. Both Intermittent and Constant pain. There were no associations with synovitis severity and reporting Intermittent Pain only vs. Both Intermittent and Constant pain.

CONCLUSION: Knee synovitis measured via US is associated with higher levels of patient-reported measures of pain, especially in late stage knee OA. Patients with more severe synovitis are more likely to report constant pain than a combination of constant and intermittent pain or intermittent pain only. MSK-US may improve our understanding of the relationship between synovitis and the experience of constant vs. intermittent knee pain phenotypes.

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**ASSOCIATIONS BETWEEN CONVENTIONAL MRI-BASED SUBCHONDRAL TRABECULAR BIOMARKERS AND TIBIOFEMORAL SUBCHONDRAL BONE 3D MORPHOLOGY CHANGES: AN EXPLORATORY ANALYSIS FROM OSTEOARTHRITIS INITIATIVE (OAI)**

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INTRODUCTION: Although subchondral trabecular changes has been shown to be associated with worse osteoarthritis outcomes in the knee joint, the potential associations between the subchondral trabecular biomarkers and bone surface changes in the knee has not been studied thoroughly.

OBJECTIVE: To study the potential associations between baseline conventional MRI-based subchondral trabecular biomarkers and tibial and femoral subchondral bone 3D morphology changes over 24 months.

METHODS: Available data of the 600 subjects in a nested case-control study (FNIH osteoarthritis [OA] biomarkers consortium) within the Osteoarthritis Initiative were extracted from the study database (including the available measurements of the subchondral bone 3D morphology metrics in different subregions of the knee at baseline and 24-month visit). Baseline knee MRI (IW sequence) of subjects were reassessed to determine conventional MRI-based subchondral trabecular biomarkers (thickness [cTbTh], spacing [cTbSp], connectivity density [cConnD], and bone-to-total volume ratio [cBV/TV]), using an in-house framework (independent variables). Associations between these biomarkers and baseline 3D morphology measurements of subchondral bone and their change over 24 months (defined with the Relative Change Index) were studied using linear (baseline) and logistic (follow-up) regression models, adjusted for relevant covariates.

RESULTS: Out of the 600 subjects in this study, 353 (58.8%) were female (mean age: 61.55±8.88). Study of the associations of subchondral trabecular biomarkers and bone 3D morphology in the baseline showed that higher cTbSp and lower cBV/TV were associated with lower bone surface areas in femoral and tibial ($\beta$:-0.59[-1.00--0.19] and $\beta$:4.53[-0.13-9.18], respectively) subregions. Moreover, higher cBV/TV in medial was associated with higher odds of changes in the tibial surface area of bone over 24 months (OR:1.24[1.12-1.37]). Conventional MRI-based subchondral trabecular biomarkers were not associated with bone vectors in this study.

CONCLUSION: Our study showed that lower cTbSp and higher cBV/TV are associated with higher bone surface area in the knee, while higher cBV/TV in the medial (24% [12-37%]) tibia is also associated with higher odds of medial tibial bone surface worsening over follow-ups. These findings suggest that measuring certain conventional MRI-based subchondral trabecular biomarkers may have predictive value for longitudinal prediction of bone surface changes in the knee. These findings highlight the potential roles of changes in subchondral trabecular architecture in OA development and progression.

SPONSOR: N/A
DICLOSURE STATEMENT: A. Guermazi is Consultant to TissueGene, Roche, Galapagos, MerckSerono, AstraZeneca, and Pfizer. A. Guermazi and F. Roemer are shareholders of Boston Imaging Core Lab, LLC. Other authors declare no competing interests specifically related to results of this work.
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**CONVENTIONAL MRI-BASED SUBCHONDRAL TRABECULAR BIOMARKERS AND THEIR ASSOCIATION WITH VOLUMETRIC MEASUREMENTS OF KNEE ARTICULAR CARTILAGES AND MENISCI: A LONGITUDINAL ANALYSIS FROM OSTEOARTHRITIS INITIATIVE (OAI)**

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INTRODUCTION: There is a growing body of evidences that subchondral trabecular biomarkers may play roles in predicting knee OA outcomes. However, the timing of subchondral trabecular architecture changes, compared to cartilage or meniscus damages in the cascade of osteoarthritis (OA) development is yet to be studied.

OBJECTIVE: To study the associations between conventional MRI-based subchondral trabecular biomarkers and volumetric measurements of knee meniscus and cartilage at baseline and their worsening over 12 and 24 months, using the FNIH OA biomarkers consortium.

METHODS: Available data and images of the 600 subjects in the FNIH OA biomarkers consortium (a nested case-control study within Osteoarthritis Initiative) were extracted from the online database. Baseline knee MRI (IW sequence) were evaluated using an in-house framework for image analysis, to determine conventional MRI-derived trabecular thickness (cTbTh), spacing (cTbSp), connectivity density (cConnD), and bone-to-total ratio (cBV/TV, independent variables). Moreover, the available measurements for medial and lateral volumes of cartilages and meniscus using baseline and 12- or 24-month knee MRI were extracted from the OAI database and the baseline volumetric measurements and their worsening over 12 or 24 months (defined using the Relative Change Index) were used in this analysis as dependent variables. Association between conventional MRI-based subchondral trabecular biomarkers and volumetric measurements of meniscus and cartilages were studied using linear and logistic regression models, adjusted for relevant confounders.

RESULTS: Subjects in the FNIH OA biomarkers consortium study had a mean age of 61.55±8.88 years with a mean BMI of 30.72±4.78 (58.8% of subjects were female). In the baseline models, higher cTbTh ($\beta$:4.53[1.52-7.54]), lower cTbSp ($\beta$:-3.02[-5.31--0.73]), and higher cBV/TV ($\beta$:46.93[21.13-72.74]) were associated with higher volumes of ipsilateral meniscuses. In the follow-up models, higher cBV/TV was associated with increased odds of medial tibia cartilage volume worsening over 12 months (OR:1.17[1.07-1.29]).

CONCLUSION: Higher cBV/TV concurrent with lower cTbSp are associated with higher meniscus volumes at baseline. Moreover, higher cBV/TV is linked with higher odds of (medial tibial) cartilage volume worsening over 12 months. Trabecular biomarkers and bone-to-total ratio (measured in conventional MRI) may be a risk factor for cartilage and meniscus volume loss, though levels of associations are modest. This finding shows the potential roles of trabecular architecture changes in the cascade of events in OA pathogenesis.

SPONSOR: N/A
DICLOSURE STATEMENT: A. Guermazi is Consultant to TissueGene, Roche, Galapagos, MerckSerono, AstraZeneca, and Pfizer. A. Guermazi and F. Roemer are shareholders of Boston Imaging Core Lab, LLC. Other authors declare no competing interests specifically related to results of this work.
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**CONVENTIONAL MRI-BASED SUBCHONDRAL TRABECULAR BIOMARKERS AS PREDICTORS OF KNEE OSTEOARTHRITIS PROGRESSION: DATA FROM THE OSTEOARTHRITIS INITIATIVE**

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INTRODUCTION: Although the associations between trabecular biomarkers with knee OA progression have been shown before, in this study we aim to study the association between symptomatic /radiographic progression of OA and quantitative measurements of subchondral trabecular architecture using the "conventional" MRI sequence.

OBJECTIVE: To evaluate the predictive value of subchondral trabecular biomarkers in "conventional" intermediate-weighted (IW) MRI sequences for predicting near-term symptomatic and structural progressions of knee osteoarthritis (OA).

METHODS: The predictive value of subchondral trabecular biomarkers in predicting knee OA progression was evaluated in 600 subjects within the FNIH OA biomarkers consortium (nested within the OAI). Subchondral trabecular biomarkers (i.e. trabecular thickness [cTbTh], spacing [cTbSp], connectivity density [cConnD], and bone-to-total volume ratio [cBV/TV]) were measured using a semi-automatic framework in the proximal medial tibia in the baseline and 24-month "conventional" coronal IW MRI images. Changes in the biomarkers from baseline to 24-month were assessed using the Reliable Change Index method. Knee OA pain and radiographic progression were evaluated by comparing the baseline WOMAC pain score and radiographic joint space width (JSW) with the 24- to 48-month values of these variables. Associations between trabecular biomarkers changes and these outcomes were studied using logistic regression models adjusted for the relevant confounders.

RESULTS: Between baseline and 24-month visit, knees with decreased cTbTh had lower (OR:0.66[0.47-0.92], p-value:0.014) and knees with decreased cTbSp (OR:1.44[1.03-2.02], p-value:0.034) or increased cBV/TV had higher (OR:1.52[1.08-2.14], p-value:0.015) odds of experiencing OA pain progression. Changes in subchondral trabecular biomarkers were not associated with radiographic knee OA progression.

CONCLUSION: Though modest, there are significant associations between "conventional" MRI-based subchondral trabecular biomarkers changes and knee OA pain progression up to 48-month follow-up in the knee joint. Despite several limitations (large and anisotropic voxels), assessment of "conventional" knee MRI sequences suggest that early changes in thickness and spacing of trabeculae are associated with symptomatic progression of knee OA over the 48-month follow-up.

SPONSOR: N/A
DICLOSURE STATEMENT: A. Guermazi is Consultant to TissueGene, Roche, Galapagos, MerckSerono, AstraZeneca, and Pfizer. A. Guermazi and F. Roemer are shareholders of Boston Imaging Core Lab, LLC. Other authors declare no competing interests specifically related to results of this work.
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**INTERACTION OF KNEE COMPARTMENTS OSTEOARTHRITIS ACCORDING TO OVER-WEIGHT STATUS: LONGITUDINAL STUDY FROM OSTEOARTHRITIS INITIATIVE (OAI)**

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INTRODUCTION: Knee consists of three compartments, medial and lateral tibiofemoral (TF) and patellofemoral (PF) compartments. Compared to lateral TF compartment, the OA of the medial TF compartment (MTFC) is more prevalent and clinically significant. In addition to the MTFC, OA in PF compartment are common. Recent reports suggested that the OA pathogenesis in the knee compartments are interrelated and compared to TF-OA, PF-OA tends to occur in younger population and is primarily associated with underlying abnormal PF morphology.

OBJECTIVE: To investigate the associations between MRI-based regional pattern (medial versus lateral) of patellofemoral osteoarthritis (PF-OA) at baseline with symptomatic, radiographic, and MRI-based progression of the medial tibiofemoral compartment (MTFC) osteoarthritis (OA) over 4 years according to the overweight status.

METHODS: MOAKS (MRI Osteoarthritis Knee Score) on the baseline subregions of the PF joint (medial and lateral) in MRIs of 600 participants from the FNIH-OA biomarkers consortium were obtained and the progression of the WOMAC pain scores and MTFC joint space narrowing (JSN) from baseline to 4-year follow-up were considered as the main outcomes of this analysis. The association between baseline regional PF-OA pattern and these outcomes were studied using regression models (adjusted for relevant confounders including demographic characteristics, knee alignment, and PF morphology measurements). Stratification analysis was also performed according to body mass index (BMI; ≥25 and <25 kg/m2).

RESULTS: At baseline, 340 (56.7%) and 255 (42.5%) subjects had features of OA at medial and lateral PF joint, respectively. Baseline medial PF-OA was associated with the MTFC WOMAC pain score and JSN progression up to 4 years (OR:1.56 [95%CI:1.09-2.23] and 1.59 [1.11-2.28], respectively). In stratification analysis, the association between medial PF-OA and MTFC WOMAC pain score and JSN progression was only seen in overweight subjects (BMI ≥25) (1.65 [1.13-2.42] and 1.63 [1.12-2.4], respectively), but not in the subjects with normal BMI (BMI<25) (0.50 [0.12-1.82] and 0.75 [0.19-2.81], respectively).

CONCLUSION: Presence of association between medial PF-OA and MTFC-OA progression only in overweight subjects even after adjustment for BMI suggest an effect modifier role for overweight status, which is also a known common "modifiable" risk factor for both PF- and TF-OA.

SPONSOR: N/A
DICLOSURE STATEMENT: A. Guermazi is Consultant to TissueGene, Roche, Galapagos, MerckSerono, AstraZeneca, and Pfizer. A. Guermazi and F. Roemer are shareholders of Boston Imaging Core Lab, LLC. Other authors declare no competing interests specifically related to results of this work.
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**QUANTITATIVE SUBCHONDRAL TRABECULAR BIOMARKERS ASSESSMENT USING CONVENTIONAL MRI SEQUENCES: THE OSTEOARTHRITIS INITIATIVE (OAI)**

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INTRODUCTION: Given the limitations of high-resolution imaging techniques (cost and unavailability), extracting information on trabecular biomarkers from "conventional" CT scans or MRI provides an opportunity for assessing these biomarkers changes in large cohort databases with existing images, such as Osteoarthritis Initiative (OAI), or routine clinical practices.

OBJECTIVE: To determine the feasibility of "conventional" MRI sequences to measure subchondral trabecular biomarkers and to evaluate the reliability and validity of assessing these biomarkers in "conventional" intermediate-weighted (IW) MRI sequences using high-resolution steady-state sequence measurements as the reference standard.

METHODS: For this study, a semi-automatic framework was developed for measuring subchondral trabecular biomarkers in the proximal medial tibia. The validity of these biomarkers measurements in "conventional" IW (matrix=384×384 pixels, FOV=140mm, thickness=3mm, TE=29ms, and TR=3,700ms) MRI sequence (i.e. trabecular thickness [cTbTh], spacing [cTbSp], connectivity density [cConnD], and bone-to-total volume ratio [cBV/TV]) was assessed in a randomly-selected set of 300 knees (from the Bone Ancillary Study within the Osteoarthritis Initiative [OAI]) by comparing to "apparent" trabecular biomarkers (using high-resolution steady-state MRI sequence), using correlation study (the Pearson, r), linear regression, and Bland-Altman graphs. The reliability of these measurements was studied after re-assessing this sample by the same trained reader after a 2-week washout period.

RESULTS: In this sample, 34(11.33%), 39(13.00%), 100(33.33%), 77(25.67%), and 40(13.33%) had Kellgren-Lawrence grade of 0, 1, 2, 3, and 4, respectively. The cTbTh, TbSp, and cBV/TV but not ConnD were modestly associated with the "apparent" trabecular biomarkers (Beta: 0.07[-0.01-0.16], p-value:0.09 | Beta: 8.97[-0.04-17.98], p-value:0.05 | Beta: 0.71[0.2-1.22], p-value:0.01 | Beta: 0.01[-0.03-0.04], p-value:0.72, respectively). Moreover, these measurements were shown to have excellent intra-reader (ICC >0.9) reliability.

CONCLUSION: Measurement of certain "conventional" MRI-based subchondral trabecular biomarkers, i.e. cTbSp and cBV/TV, have high reliability but only modest validity, compared to high-resolution steady-state MRI sequence measurements. Despite several limitations (large and anisotropic voxels), the "conventional" MRI sequences can be used to measure certain subchondral trabecular biomarkers with excellent reliability and acceptable validity. Although findings of this report need to be confirmed with future studies, given the availability of "conventional" MRI sequences, the results of this project show the potentials for using these sequences in large cohorts and clinical practice.

SPONSOR: N/A
DICLOSURE STATEMENT: A. Guermazi is Consultant to TissueGene, Roche, Galapagos, MerckSerono, AstraZeneca, and Pfizer. A. Guermazi and F. Roemer are shareholders of Boston Imaging Core Lab, LLC. Other authors declare no competing interests specifically related to results of this work.
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# CORRELATION BETWEEN TWO-YEAR LONGITUDINAL CHANGE IN MENSICAL EXTRUSION AND CARTILAGE THICKNESS IN KNEES WITH AND WITHOUT SUBSEQUENT KNEE REPLACEMENT

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INTRODUCTION: Knees progressing from early radiographic OA to knee replacement (KR) have been reported to exhibit fast cartilage loss as well as meniscus deterioration. It has, however, not been reported to what extent these changes are associated with each other.

OBJECTIVES: 1) To determine whether change in 3D meniscal measures, specifically meniscal extrusion, is associated with change in cartilage thickness over a two-year observation period, in knees with fast structural progression; 2) to assess differences between knees with and without KR.

METHODS: A nested case-control study was conducted among OAI participants: 35 case knees (52% women; age 65±7y; BMI 30±4kg/m²; KLG0/1/2: 5/8/22) with baseline KLG ≤2 had KR between 36-60 months. These were matched 1:1 by age, sex, and baseline KLG to 35 control knees (52% women; age 64±7y; BMI 30±5kg/m²; KLG0/1/2: 9/4/22) without subsequent KR. Quantitative medial meniscus measures and cartilage thickness in the central medial compartment (cMFTC) were determined from MRI at the visit just before KR, and two years before. Due to non-normally distributed data, non-parametric Spearman correlation coefficients were used to assess the association between changes in the meniscus and cartilage. Fisher's z-test was applied to explore whether correlation coefficients differed between cases and controls. P-values < 0.05 were considered statistically significant, without adjusting for multiple comparisons in this exploratory study.

RESULTS: The total sample showed small to moderate correlations between the two-year change in cMFTC thickness and in meniscal parameters (up to r=0.51; Table 1). Stronger associations were observed for positional meniscal parameters (extrusion) than for morphological ones. Figure 1 displays the relationship between cMFTC cartilage thickness and meniscus extrusion area (TA_Uncov%). The correlation coefficients appeared to be greater for cases than for controls. Yet, only the association between cMFTC cartilage thickness and TA.Uncov% extrusion differed statistically significantly between cases and controls (p=0.04).

**Table 1.** Spearman's correlation coefficients between two-year changes in cMFTC and two-year changes in respective meniscal parameters.

| | TA.Uncov% | ACdAB.Cov% | Ex.Mean | Ex.Max | Th.mean | Wid.mean |
|---|---|---|---|---|---|---|
| **total cohort** (n=70) | -0.40 (0.001) | 0.50 (0.000) | -0.43 (0.000) | -0.25 (0.037) | -0.15 (0.211) | 0.29 (0.014) |
| **controls only** (n=35) | -0.03 (0.850) | 0.29 (0.089) | -0.14 (0.430) | 0.11 (0.532) | -0.05 (0.797) | -0.10 (0.563) |
| **KR cases only** (n=35) | -0.51 (0.002) | 0.49 (0.003) | -0.49 (0.003) | -0.26 (0.132) | -0.28 (0.106) | 0.41 (0.014) |

**Abbreviations:** cMFTC: cartilage thickness in the central medial femoro-tibial compartment; TA.Uncov%: uncovered area of the TA (tibial surface of the medial meniscus) in percent; ACdAB.Cov%: overlap area between TA and ACdAB (joint surface of the tibia, consisting of the area of the cartilage surface, and denuded areas of subchondral bone if applicable) in percent; Ex.mean: mean medial extrusion distance; Ex.max: maximal medial extrusion distance; Th.mean: mean medial meniscal thickness; Wid.mean: mean medial mensical width

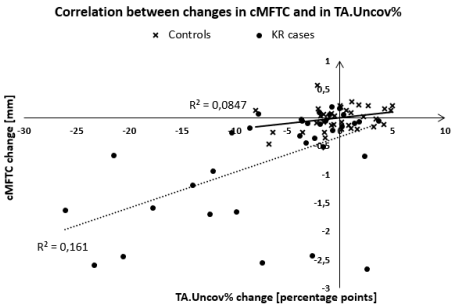


**Fig. 1.** Correlation between changes in cMFTC and in TA.Uncov%. Abbreviations: see Table 1

CONCLUSION: The only moderate correlation suggests that there are OA patients with concurrent change (or concurrent stability) in meniscal extrusion and cartilage loss, but also OAI participants who exhibit little to no change in meniscal extrusion whilst exhibiting large amounts of cartilage loss, or vice versa. A greater magnitude and range of structural change in knees undergoing subsequent KR likely explains the somewhat greater correlation in case vs. control knees.

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# CHANGES IN PATELLAR CARTILAGE AFTER ACL RECONSTRUCTION AS DETECTED USING $T_2$ RELAXATION TIMES

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INTRODUCTION: ACL injuries have been shown to increase the risk of OA[1]. Past research has focused on femorotibial cartilage with less investigation on the patellar cartilage following ACL injuries and reconstructive surgery. Focally elevated quantitative MRI $T_2$ relaxation times in the femoral cartilage have been seen as early as 3 months post ACL reconstruction (ACLR) surgery[2]. We hypothesize similar differences in $T_2$ relaxation times in patellar cartilage $T_2$ relaxation times.

OBJECTIVE**:** To determine if patellar cartilage showed a difference in $T_2$ relaxation times between healthy controls and ACL-injured subjects following ACLR surgery.

METHODS**:** 10 ACL-reconstruction participants (5F, 39±12 yrs., BMI: 23±1.5) and 10 controls (5F, 37±13 yrs., BMI: 23 ± 1.5) were included. The ACL-reconstructed and their contralateral knees, along with the right knee of the controls were scanned at 3 weeks, 3 months, and 9 months post-surgery. All subjects were scanned on a 3T MRI scanner, and qDESS images were acquired to calculate $T_2$ relaxation times[3]. Patellar cartilage was manually segmented at each timepoint and used to define the region of interest for $T_2$ maps. 2D $T_2$ projection maps were created by projecting an average of through-thickness $T_2$ relaxation times. Differences in average $T_2$ relaxation times were calculated over three intervals: (3 months – 3 weeks), (9 months – 3 months), and (9 months – 3 weeks). A One-Way Analysis of Variance test with a Tukey Post- Hoc test and $\alpha = 0.05$ was used to test for differences of $T_2$ between the different time points and the injured, control, and contralateral knees.

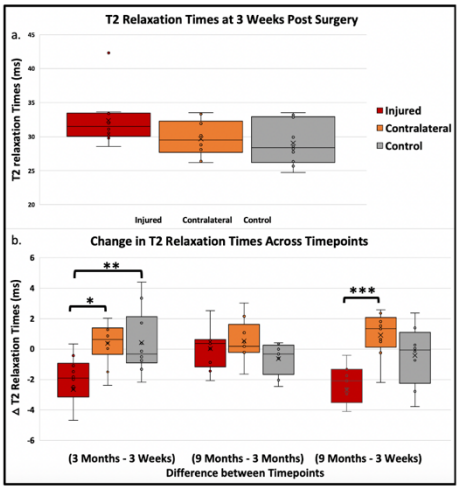


**Fig. 1**: [a] Total patellar cartilage averages at 3 weeks in the injured, contralateral, and control knee. [b] Change in $T_2$ relaxation times in the ACL injured, contralateral, and control knees. (*p = 0.010, ** p = 0.016, *** p = 0.001).

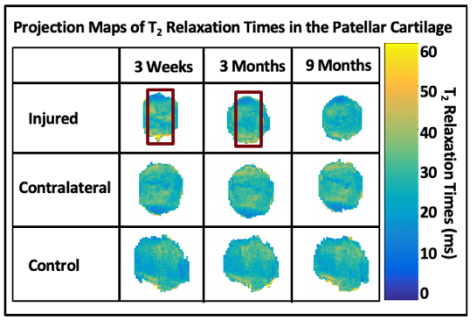


**Fig 2**: 2D projection maps for the ACL-injured, contralateral, and control knee. The most significant change in $T_2$, in the injured knee, is outlined by the red box.

RESULTS**:** Three weeks post-surgery, the injured knee had elevated $T_2$ relaxation times approaching statistical significance compared to the contralateral and control knees [Fig. 1a]. From 3 weeks to 3 months, the injured knee had a significantly larger decrease in $T_2$ relaxation times than the contralateral ($p = 0.01$) and control knees ($p = 0.016$), but not a significantly different decrease or increase from 3 months to 9 months [Fig. 1b]. The decrease in $T_2$ from 3 weeks to 3 months was predominantly seen near the middle of the patellar cartilage in the injured knee [Fig. 2].

CONCLUSION**:** Comparing the injured knee to the contralateral and control knees, the patellar cartilage $T_2$ variations show that the higher patellar cartilage $T_2$ relaxation times at 3 weeks post ACLR surgery are temporary. Furthermore, three months after surgery, the patellar cartilage of the injured knee had similar $T_2$ relaxation times to the contralateral and control knees. This longitudinal $T_2$ pattern post-ACL tear is markedly different from what is seen in the femoral cartilage, where the $T_2$ relaxation times continue to be elevated at 3 months and 9 months, suggesting that patellar and femoral cartilage behave differently following ACLR surgery.

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DISCLOSURES: AC has consulted for Subtle Medical, Chondrometrics, Edge Analytics, Culvert Eng., ICM.
REFERENCES**:** 1. Øiestad, AJSM 2009, 3. Black, ISMRM 2020, 4. Sveinsson, MRI 2017
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## GADOLINIUM-FREE ASSESSMENT OF SYNOVITIS USING DIFFUSION TENSOR IMAGING

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INTRODUCTION: Evidence suggests that synovitis is associated with OA progression and osteophyte (OP) development. Synovitis can be quantified by the volume transfer coefficient ($K^{trans}$) between blood plasma and extracellular extravascular space, derived from dynamic contrast-enhanced (DCE) MRI using gadolinium-based contrast agent (GBCA). Diffusion Tensor Imaging (DTI) is a non-invasive MRI-based method that shows great potential to detect synovitis by measuring diffusion properties of water molecules within the inflamed synovium.

OBJECTIVE: Evaluate the feasibility of using DTI to assess synovitis without GBCA by 1) determining if DTI parameters within the synovium correlate with $K^{trans}$ and 2) determining if DTI and DCE parameters adjacent to OPs vary by semi-quantitative OP grading (MOAKS).

METHODS: 16 knees with a clinical diagnosis of OA from 11 subjects (7 female, age: 54 ± 12 years, BMI: 26.6 ± 3.9) were analyzed. Simultaneous bilateral 3T MRI (GE Signa PET-MR, GE Healthcare, Waukesha, WI) was performed at a single timepoint, which included DESS, matching pre- and post-contrast 3D fat-suppressed (FS) SPGR sequences, and DCE sequences acquired during GBCA administration. The synovium was semi-automatically segmented by a shuffle subtraction of the pre- and post-contrast 3D FS SPGR sequences, and voxelwise maps of $K^{trans}$ were created by extended Tofts modelling of the DCE data. A musculoskeletal (MSK) radiologist identified and graded OPs using the MOAKS system, and manually defined a region of interest (ROI) surrounding each OP. The synovial segmentation, OP ROIs, and $K^{trans}$ map were non-rigidly registered to the high resolution DESS image. OP adjacent ROIs were defined as the intersection of the synovium segmentation and each OP ROI. DTI data was acquired using a single-shot DWI-EPI sequence, with 3 scans at b = 0 s/mm$^2$ and 15 directional scans at b = 400 s/mm$^2$. The diffusion images were denoised and non-rigidly registered to the DESS image using a manually segmented synovium mask, drawn by a MSK radiologist. The diffusion tensor was calculated and used to create voxelwise maps of Mean Diffusivity (MD) and Fractional Anisotropy (FA). Correlations between diffusion parameters (MD and FA) and $K^{trans}$ were assessed with Pearson's correlation coefficients and simple linear regression analysis, while differences in parameters based on OP MOAKS grade were analyzed by one-way ANOVA.

RESULTS: Within the semi-automatic synovial segmentation, MD had a significant positive correlation with $K^{trans}$ values ($r = 0.79$, $p < 0.001$), while FA had a significant negative correlation ($r = -0.72$, $p = 0.0026$). For each SD increase in $K^{trans}$, MD increased by 0.00013 (approximately 7% of the median MD value) and FA decreased by 0.020 (approximately 6% of the median FA value). A total of 67 OPs were identified (44x MOAKS Grade 1 - Small, 20x Grade 2 - Medium, 3x Grade 3 - Large). Within OP adjacent ROIs, MD and FA had weak correlations with $K^{trans}$ that were not significant ($r = 0.11$, $p = 0.35$ and $r = -0.26$, $p = 0.03$, respectively). MD, FA, and $K^{trans}$ values adjacent to OPs did not vary significantly when separated by MOAKS grade ($p = 0.43$, $p = 0.56$, $p = 0.21$, respectively).

CONCLUSION: MD and FA correlations with $K^{trans}$ within the synovium segmentation suggest that DTI may be useful for assessing intensity of synovitis without administering GBCA. Increased MD and decreased FA may reflect the microstructural and biochemical changes associated with inflammation that are known to occur in the synovium. However, DTI appears unable to assess synovitis in focal regions, potentially due to its inherently low image resolution and the small ROI size. Additionally, quantitative values for intensity of adjacent synovitis do not appear to vary with semi-quantitative grade of OPs.

SPONSOR: GE Healthcare
DISCLOSURES: None
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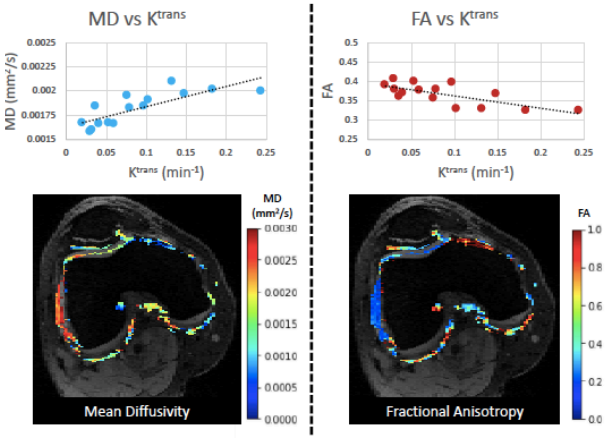


Top: Graphs of MD and FA correlations with $K^{trans}$ within the synovium
Bottom: Representative MD and FA maps, overlaid on axial view of DESS image

**A DEEP-LEARNING-BASED TECHNIQUE FOR THE QUANTITATIVE ANALYSIS OF FEMOROTIBIAL BONE AND OSTEOPHYTES – PRELIMINARY DATA FROM THE OAI**

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INTRODUCTION: Osteophytes (OPs) are prominent features in knee OA, and are used to define definite radiographic knee OA. OPs have been suggested to be associated with pain and subsequent knee replacement. Currently, most studies investigating the role of OPs rely on semi-quantitative scorings from x-ray or MRI. A quantitative analysis of OPs from MRI may provide greater sensitivity than scoring-based methodologies: This requires segmentation, which is time-consuming when performed manually. Convolutional neural networks such as the U-Net may allow automating this task.

OBJECTIVE: To examine the agreement between automated, U-Net-based segmentation of distal femoral and proximal tibial bone, and OPs, vs. manual segmentation in knees with radiographic OA.

METHODS: The target sample comprised coronal FLASH MRI from 227 right knees with radiographic OA (KLG 2/3/4: n=106/76/45, women/men: n=141/86, age: 63±9y) from the Osteoarthritis Initiative (OAI). The distal femur and proximal tibia were thus far manually segmented in 45 of the 227 knees (KLG 2/3/4: n=26/15/4). 2D U-Nets were trained using 4 labels (femoral bone, femoral OPs, tibial bone, tibial OPs, training/validation set n=25/10). The agreement between automated and manual segmentations was evaluated on 10 knees (test set).

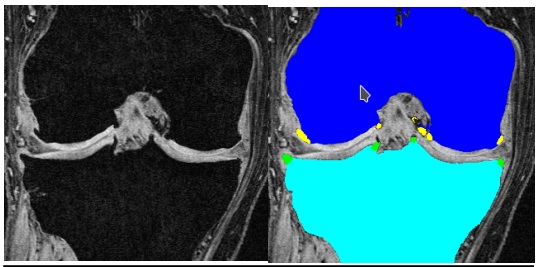

Fig. 1: Coronal FLASH MRI (left) with automated bone and osteophyte segmentation (right)

RESULTS: The preliminary results showed good agreement between manual and automated bone segmentations, with a Dice Similarity Coefficient (DSC) of 0.98±0.00 for the distal femoral and 0.98±0.00 for the proximal tibial bone. The agreement observed for femoral/tibial osteophytes was notably lower, with DSCs of 0.48±0.06 and 0.38±0.14, respectively.
Volumes did not differ significantly between automated vs. manual segmentations for the distal femoral (178.9±20.5cm³ vs. 178.5±20.8 cm³, p=0.57) and proximal tibial bones (125.2±22.9cm³ vs. 124.2±22.3cm³, p=0.06) and were highly correlated between both approaches (femur: r=0.99, tibia: r=1.0). The OP volume, in contrast, was significantly underestimated by automated segmentation, both in the distal femur (2.1±0.8cm³ vs. 3.8±2.3cm³, p=0.01) and in the proximal tibia (0.7±0.3cm³ vs. 1.7±0.9cm³, p<0.01). Correlations were r=0.86 for femoral and r=0.46 for tibial OP volume.

CONCLUSION: These preliminary results suggest that an automated, U-Net-based approach is capable of providing accurate segmentation of distal femoral and proximal tibial bone. The low agreement obtained between manual and automated osteophyte segmentations can most likely be attributed to the highly variable shape, size, and location of the osteophytes. Hence, a greater number of manually segmented knees appears to be necessary for adequate training of the U-Net, before applying the method to investigate the role of quantitatively measured OP volume in knee OA.

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**THE EFFECTS OF LIMB REALIGNMENT SURGERY ON MRI MEASURES OF KNEE INFLAMMATION IN PATIENTS WITH MEDIAL TIBIOFEMORAL OSTEOARTHRITIS**

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INTRODUCTION: Effusion-synovitis and BM lesions measured by MRI are common signs of local inflammation in knee OA; both are associated with increased pain and risk of OA progression. Medial opening wedge high tibial osteotomy (HTO) aims to limit OA progression by lessening aberrant loads on the medial compartment in patients with medial JSN due to knee OA and varus alignment. While it is plausible that HTO may affect potential inflammatory responses to joint loading, the effects of HTO on measures of knee inflammation remain unclear.

OBJECTIVE: To compare MRI measures of effusion synovitis and BM lesion volume in the surgical and contralateral limbs before and 1 year after unilateral medial opening wedge HTO.

METHODS: We evaluated 35 patients [pre-operative KLG = 3, age = 54 ± 6 years, 27 males (79%), body mass index = 29.8 ± 4.4 kg/m$^2$] with medial JSN due to knee OA and varus alignment who were undergoing HTO in the most symptomatic knee. 3-Tesla MRIs were acquired on both knees pre and 1-year after HTO, at least 6 weeks after removal of hardware. Using a 3D DESS sequence (160 slices, 0.7mm thickness, 0.4 x 0.4 x 0.7mm voxel) effusion-synovitis and BM lesion volume were manually segmented by a single reader blinded to limb and time by masking the proximal tibia on all images. Synovitis was segmented in the supra- and para-patellar regions. Due to masking, BM lesions were only segmented in medial and lateral compartments of the femur. Surgical and contralateral knees were compared before and after HTO using 2-way repeated measures ANOVA and post-hoc simple main effects with Bonferroni corrections were run following significant interactions.

RESULTS: In the surgical limb, the mechanical axis angle had a mean change (95% CI) of 7.13 (5.90. 8.47). A statistically significant (p=0.034) limb-by-time interaction was detected for knee effusion-synovitis volume. Effusion-synovitis volume was significantly larger pre-HTO and significantly decreased post-HTO in the surgical knee only. The mean change (95% CI) was -1924.63
(-3638.85, -210.41) in the surgical knee and 350.67 (-750.62, 1451.96) in the contralateral knee. BM lesion volume in the medial compartment of the surgical limb was larger than the contralateral limb before surgery, but were highly variable and did not demonstrate a statistically significant limb-by-time interaction.

CONCLUSION: MRI measures of knee inflammation are greater in the surgical limb compared to the non-surgical limb in patients with medial compartment JSN due to knee OA and varus alignment. Reduction of effusion-synovitis volume 1-year after HTO surgery suggests that effusion-synovitis may be sensitive to changes in knee loading. Further research is needed to determine if BM lesion volumes are less sensitive to changes in load or may take longer to occur.

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## COMPARISON OF 24-MONTH RESPONSIVENESS TO CHANGE BETWEEN TIBIOFEMORAL 3D JSWx ON WEIGHT-BEARING CT WITH RADIOGRAPHIC 2D JSWx

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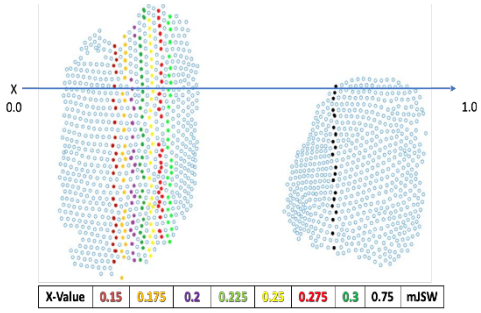
INTRODUCTION: Limitations of 2D radiographic JSW, such as the dependence on x-ray beam alignment with the medial tibial plateau, along with the temporal and spatial heterogeneity of structural progression of knee OA, limits the responsiveness in measuring structural progression (3-year standardized response means (SRM) range from -0.03 to -0.74). 3D JSW measured on weight-bearing CT (WBCT) 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 compare the responsiveness of 3D JSWx on WBCT vs. 2D JSWx over 24 months.

METHODS: Fixed flexion PA radiographs were acquired as part of the Multicenter Osteoarthritis Study (MOST) and JSWx was calculated at each mediolateral location as has been described previously. Fixed-flexion WBCT images of the knee were acquired using a commercial scanner (LineUP, CurveBeam, Warrington, PA). The scanner produced pulsed cone-beam x-ray on a 30×30 cm amorphous silicon flat-panel detector over a 360° projection angle (total scan time 32 seconds; effective radiation dose 0.1 mSv). A 3D dataset with an isotropic resolution of 0.37mm was reconstructed from cone beam projections. Tibiofemoral bony geometries were obtained through semi-automated segmentation of the WBCT images as triangulated 3D surface meshes (Seg3D Version 2.2.1). The 3D JSW was then defined as the Euclidean distance from the center of each triangulated face to the opposing surface along its normal direction. 3D JSWx was defined as the minimum value for JSW in the posteroanterior line at each mediolateral x location from x=.150–.750 (Figure). Responsiveness to change was defined by the standardized response mean (SRM=mean change/SD change) for 2D JSWx and 3D JSWx. Responsiveness was compared between 2D JSWx and 3D JSWx using t-tests when SRM values were distributed normally and by Wilcoxon signed rank test when not.

RESULTS:
At the time of these analyses, paired 2D and 3D JSWx measurements were available for 329 knees imaged at the 144- and 168-month MOST clinic visits (56.8% women).

**Table 1:** Responsiveness to Change in 2D and 3D JSWx over 24 months




| JSWx Location | XR SRM (95% CI) | | WBCT SRM (95% CI) | | p-value |
|---|---|---|---|---|---|
| minJSW | 0.11 | (0.01, 0.21) | -0.05 | (-0.16, 0.06) | 0.0331 |
| .150 | -0.12 | (-0.22, -0.02) | -0.21 | (-0.31, -0.11) | 0.0120 |
| .175 | -0.12 | (-0.22, -0.02) | -0.24 | (-0.34, -0.14) | 0.0099 |
| .200 | -0.13 | (-0.23, -0.03) | -0.20 | (-0.31, -0.10) | 0.1436 |
| .225 | -0.11 | (-0.22, -0.01) | -0.22 | (-0.32, -0.12) | 0.0355 |
| .250 | -0.14 | (-0.24, -0.03) | -0.17 | (-0.27, -0.07) | 0.5218 |
| .275 | -0.11 | (-0.22, 0.00) | -0.14 | (-0.24, -0.03) | 0.6233 |
| .300 | -0.12 | (-0.23, -0.02) | -0.14 | (-0.25, -0.04) | 0.6461 |
| .750 | -0.12 | (-0.23, -0.01) | -0.12 | (-0.22, -0.02) | 0.7973 |

CONCLUSION: 3D JSWx is more responsive to 24-month change in the medial tibiofemoral compartment than radiographic JSWx. Use of 3D JSWx measured on WBCT may permit detection of tibiofemoral change more easily over this duration, expediting assessment of structural outcomes without increasing radiation dose or acquisition time.

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**SUB-REGIONAL TIBIOFEMORAL 3D JOINT SPACE WIDTH (3D JSW) MEASURED ON WEIGHT-BEARING CT IS HIGHLY RESPONSIVE TO CHANGE OVER 24-MONTHS**

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INTRODUCTION: Imaging markers with greater responsiveness to change can expedite the pace of scientific discovery through allowing shorter-duration clinical trials, saving time and making trials more affordable for sponsors. Studies of computerized measurement of radiographic JSW have reported standardized response means (SRM) of -0.26 (95% CI: -0.13, -0.38) over 1–2 years and -0.68 (-0.31, -1.06) for studies of greater than 2 years. In contrast, quantitative cartilage thickness on 3D MRI has greater responsiveness to OA disease progression, with SRM as high as -0.84 over 1 year. While assessed in 3D, MRI is generally acquired non-weight-bearing, which may hinder responsiveness in cases of cartilage swelling or altered meniscal position. 3D JSW measured on weight-bearing CT (WBCT) images holds potential to enhance responsiveness by overcoming limitations of 2D loaded and 3D non-loaded measures.

OBJECTIVE: To determine responsiveness of a novel measure of tibiofemoral 3D JSW on WBCT by articular sub-region and baseline KL grade.

METHODS: This study was conducted ancillary to the 144-month and 168-month clinic visits of the Multicenter Osteoarthritis Study (MOST). WBCT images of the knee were acquired in a fixed-flexion stance using a commercial scanner (LineUP, CurveBeam, Warrington, PA). The scanner produced pulsed cone-beam x-ray on a 30×30 cm amorphous silicon flat-panel detector over a 360° projection angle (total scan time 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 cone beam projections. Tibiofemoral geometries were obtained through semi-automated segmentation of WBCT images as triangulated 3D surface meshes (Seg3D Version 2.2.1). 3D JSW was defined as the distance from the center of each triangulated face to the opposing surface along its normal direction in the following tibiofemoral subregions: central medial and lateral femur (CMF/CLF) and tibia (CMT/CLT), and anterior and posterior tibia (AMT/ALT, PMT/MLT). Responsiveness to change was defined as the SRM (mean change/SD change over 24 months) for the maximal change within each subregion.

RESULTS:
At the time of these analyses, sub-regional 3D JSW data were available for 248 knees.

**Table 1:** Responsiveness of Maximum Change in 3D JSW in Tibiofemoral Subregions over 24 Months

| Sub-Region | All Participants (N=248) SRM (95% CI) | Baseline KL0 (N=130) SRM (95% CI) | Baseline KL1 (N=55) SRM (95% CI) | Baseline KL2 (N=48) SRM (95% CI) | Baseline KL3 (N=15) SRM (95% CI) |
|---|---|---|---|---|---|
| **CMF** | -2.68 (-2.94, -2.42) | -2.70 (-3.08, -2.31) | -2.49 (-3.24, -1.73) | -2.97 (-3.52, -2.42) | -2.50 (-3.76, -1.25) |
| **CLF** | -2.88 (-3.19, -2.57) | -3.22 (-3.65, -2.79) | -2.30 (-3.11, -1.49) | -2.75 (-3.22, -2.28) | -3.44 (-5.12, -1.76) |
| **CMT** | -1.88 (-2.03, -1.72) | -1.83 (-2.04, -1.62) | -2.03 (-2.42, -1.65) | -1.99 (-2.36, -1.61) | -1.71 (-2.19, -1.23) |
| **CLT** | -2.00 (-2.17, -1.82) | -2.09 (-2.33, -1.85) | -2.16 (-2.56, -1.77) | -1.75 (-2.10, -1.41) | -1.80 (-2.44, -1.16) |
| **AMT** | -1.76 (-1.93, -1.59) | -1.68 (-1.92, -1.43) | -1.78 (-2.07, -1.49) | -1.98 (-2.45, -1.50) | -1.56 (-2.47, -0.65) |
| **ALT** | -1.75 (-1.92, -1.57) | -1.79 (-2.04, -1.55) | -1.61 (-1.96, -1.25) | -1.71 (-2.14, -1.28) | -1.76 (-2.83, -0.69) |
| **PMT** | -1.95 (-2.14, -1.75) | -2.05 (-2.38, -1.72) | -1.76 (-2.27, -1.25) | -1.92 (-2.28, -1.56) | -2.07 (-2.91, -1.23) |
| **PLT** | -2.03 (-2.25, -1.81) | -2.29 (-2.60, -1.98) | -1.64 (-2.19, -1.10) | -1.96 (-2.37, -1.56) | -1.96 (-3.23, -0.69) |

CONCLUSIONS: Maximal change in 3D JSW appears to have substantially greater responsiveness than other measures of tibiofemoral change over 24-month follow-up. Responsiveness of this 3D JSW imaging marker remains high across medial/lateral tibiofemoral sub-regions and is relatively stable across baseline KL grades.

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**LONGITUDINAL CHANGE IN THIGH SUBCUTANEOUS (SCF) AND INTER-MUSCULAR FAT (IMF) ANATOMICAL CROSS-SECTIONAL AREAS PRIOR AND CONCURRENT TO CLINICALLY IMPORTANT WORSENING OR IMPROVEMENT IN WOMAC-KNEE FUNCTION – DATA FROM THE OAI**

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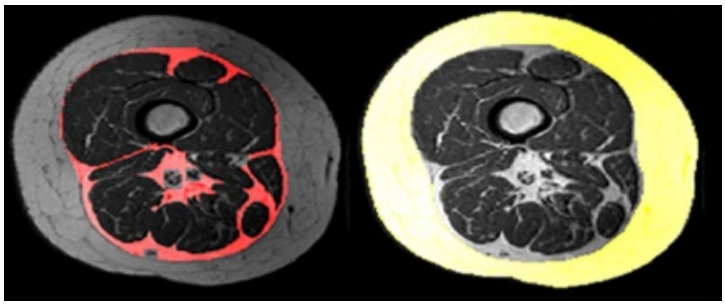
INTRODUCTION: The specific role of muscle, subcutaneous fat (SCF) and intermuscular fat (IMF) in knee OA, and specifically its relationship with knee function is not well understood. Few studies have reported a positive concurrent association between change in muscle strength and worsening/improvement in knee function based on the WOMAC function score. We recently reported that change in muscle strength, and in specific strength (SMS), but not in muscle anatomical cross-sectional areas (ACSAs), are related to longitudinal change in knee function.

OBJECTIVE: To test whether a clinically relevant change in knee function is associated with a preceding or concurrent change in thigh SCF or IMF ACSAs, as indirect measures of muscle fat, related to specific strength.

METHODS: We studied 2675 Osteoarthritis Initiative (OAI) participants who had baseline, year 2 (Y2), and Y4 follow-up data on knee function, maximal muscle strength, and thigh MRIs (Fig. 1). The participants were divided into a) those with worsening (≥6 [of 68] WOMAC function units = minimally clinically important difference (MCID)) from Y2→Y4; b) those with improvement (≥6) from Y2→Y4; c) without relevant change from Y2→Y4. Of these, the first 25 men and 25 women in each group (total n=150) were studied here. Thigh ACSAs of and IMF (Fig. 1, red labelled) and SCF (yellow labelled) were segmented semi-automatically. To test for longitudinal differences between the 3 groups in the concurrent (Y2→Y4) and preceding (BL→Y2) periods, multivariate analysis of variance (MANCOVA) was used. No adjustment of multiple parallel testing was done in this exploratory study.



RESULTS: During Y2→Y4 (the concurrent interval), SCF increased by 3.4% (95% CI [-1%, 7%]) in knees with functional worsening, and decreased by -2.3% (-6%, 1%) in those with improvement; it increased by 1.9% (-1%, 5%) in those without relevant function change. IMF concurrently increased by 2.3% (-1%, 5%) in knees with worsening, decreased by -3.8% (-7%,-1%) in knees with improvement, and increased by 1.6% (-2%, 5%) in those without relevant change. The reduction of IMF in knees with functional improvement was significantly greater than that in those without change (p=0.02). During BL→Y2 (the predictive interval), SCF decreased by -2.6% (-6%, 1%) in knees with functional worsening, decreased by -0.7% (-4%, 2%) in those with improvement, and increased by 1.1% (-2%, 4%) in those without relevant change. During this period, IMF decreased by -1.6% (-4%, 1%) in knees with functional worsening, increased by 1.9% (-1%, 5%) in those with improvement, and decreased by -0.3% (-3%, 3%) in those without relevant change. During this predictive observation interval, no statistically significant longitudinal differences in either SCF or IMF were observed in knees with worsening or improvement vs. those without relevant change. In the group with worsening, significant correlations were found in changes of SCF and IMF prior ($r^2$=0.31; p=0.03) and concurrent ($r^2$=0.30; p=0.04) to knee function change, but not between that of SMS and SCF or IMF. In the group with improvement, significant correlations were found between SCF and IMF prior ($r^2$=0.34; p=0.02) and concurrent ($r^2$=0.37; p<0.01) to a change in knee function, and between SCF and SMS ($r^2$=0.30, p=0.04) prior to (but not concurrent with) a change in knee function.

CONCLUSION: Thigh fat tissue content (SCF and IMF) increased concurrently (Y2→Y4) in a group with functional (WOMAC) worsening, and decreased in a group with functional improvement. The reduction in IMF in those with improvement was greater than in those without relevant function change These changes concurred (but did not strongly correlate) with loss of specific muscle strength (strength /ACSA) in those with functional worsening, and gain in specific strength in those with improvement, potentially reflecting an increase/decrease in non-contractile tissue within the muscle. Yet, neither longitudinal change in SCF nor IMF appeared to be predictive of future function change.

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**NON-CONTRAST MRI OF SYNOVITIS USING QUANTITATIVE DESS IN THE KNEE**

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INTRODUCTION: Synovitis, inflammation of the synovial membrane surrounding synovial fluid, is an important component of OA and is thought to play a key role in disease progression. Synovitis is typically evaluated using T1-weighted dynamic contrast-enhanced MRI (DCE MRI) but is not widely utilized in clinical imaging due to its increased time, complexity, cost, and risks. Quantitative double-echo in steady state (qDESS) has previously been proposed as a non-contrast method for detection of synovitis[1].

OBJECTIVE: To determine whether non-contrast qDESS can replace DCE for imaging of synovitis.

METHODS: We scanned both knees of 11 patients (n=11) with clinically diagnosed moderate to severe OA in at least one knee on a 3.0T MRI scanner (GE Healthcare). All subjects were scanned with two bilateral 3D qDESS sequences, one of which utilized a low diffusion gradient (2 cycles/pixel, DESS low) and the other of which used a high diffusion gradient (20 cycles/pixel, DESS high). Gold standard bilateral fat suppressed DCE images were also acquired following intravenous injection of a gadolinium-based contrast agent (Gadovist; Bayer, Leverkusen, Germany). The first and second DESS echoes were then combined to form hybrid images according to the formula $hybrid\ image = echo_1 - \beta * echo_2$ where β is a weighting factor equal to 2.8 utilized to null synovial effusion[2]. DESS high, DESS low, and DCE images were then randomized, blinded, and put into three reader sets with 22 images in each. Four musculoskeletal radiologists were recruited to grade images for synovitis. Readers were asked to grade an overall impression of synovitis as well as synovitis at four sites in the knee[3]: the medial and lateral parapatellar recesses, intercondylar notch, and suprapatellar pouch. Grading of synovitis utilized a four-point scale from 0 to 3, where 0 indicated no synovitis and 3 indicated severe synovitis. Readers also rated their diagnostic confidence on a scale from 0 to 3, where 0 represented no confidence and 3 represented high confidence. We calculated linearly weighted Gwet's AC2 to evaluate agreement between DCE and DESS gradings, as well as inter-rater agreement. Mean diagnostic confidence was also calculated.

RESULTS: All methods showed good inter-rater agreement; highest agreement was seen for DCE (AC2=0.81) followed by DESS low (AC2=0.74) and DESS high (AC2=0.64). Similarly, good agreement with DCE for the overall impression of joint synovitis was observed in DESS low (AC2=0.74), and DESS high (AC2=0.66). DCE had the highest diagnostic confidence with a mean rating of 2.73 ± 0.47, followed by DESS low with a mean rating of 2.36 ± 0.65, with DESS high having the lowest diagnostic confidence with a mean rating of 1.86 ± 0.70.

CONCLUSION: Both DESS low and high showed good agreement in assessment of synovitis to the reference standard DCE. In instances of disagreement between DCE and DESS scoring, DESS was largely seen to underestimate the degree of synovial thickening. This may be due to the known overestimation of synovial volume on DCE due to leakage of the contrast agent from the synovium into surrounding tissue. While DCE had higher diagnostic confidence as expected, DESS low was consistently rated with moderate to high confidence. Raters tended to only have low to moderate confidence in DESS high. This work shows the potential of the DESS sequence for non-contrast imaging of synovitis. Such a method could greatly enhance clinical and research evaluation of synovitis in OA.

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REFERENCES: (1) Fan AP, Fong G, Sveinsson B, et al. Automated, non-contrast MRI for detection of synovitis using diffusion-weighted DESS. Osteoarthritis and Cartilage. 2015;23:A240-A241. doi:10.1016/j.joca.2015.02.447
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**FEASBILITY AND TEST-RETEST REPEATABILITY OF 3D JOINT SPACE MAPPING AT THE ANKLE AND HINDFOOT USING WEIGHT-BEARING CT**

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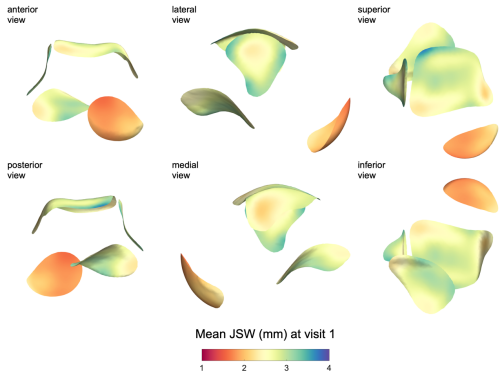
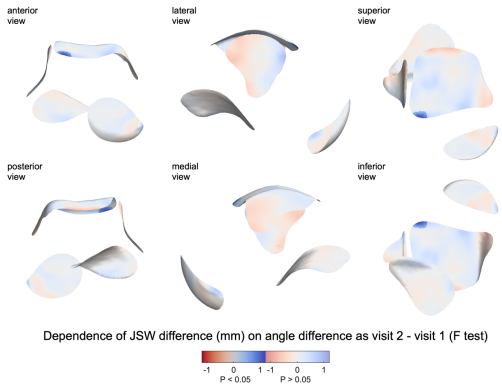
INTRODUCTION: Joint space mapping (JSM) is an image analysis technique that can measure 3D JSW distribution at human joints. It has been applied successfully at the hip and knee and is now demonstrated at the ankle and hindfoot using weight-bearing cone beam CT imaging.

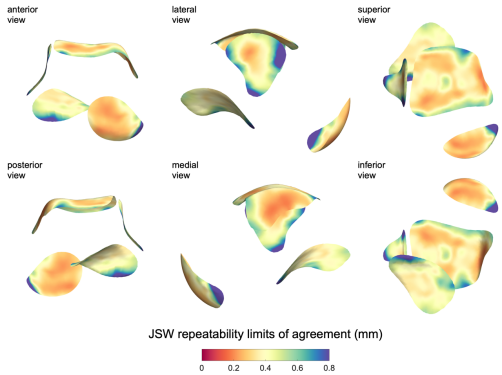
OBJECTIVE: To demonstrate (1) feasibility of JSM, (2) the effect of talocrural joint angulation, and (3) test-retest repeatability, at clinically important hindfoot and ankle articular surfaces, using weight-bearing CT.




METHODS: A convenience sample of 30 individuals with repeat weight-bearing CT examinations of both feet and ankles performed within 4 months between 2013 and 2017 were retrospectively selected with no prior constraints on joint positioning. 5 individuals were excluded with motion artefact and 2 with metal-induced artefact causing failure of the JSM technique. The mean ± SD age of the 23 study individuals was 52.7 ± 14.7 years, with 16 females and 7 males. Sides for analysis were selected to provide a mixture of features (13 left, 10 right): 11 had no metalwork; 6 various metalwork fusions in the ipsilateral foot, 6 in the contralateral foot. The mean ± SD interval between visits was 74.0 ± 29.6 days. JSM mapping was performed at the medial talocrural (mTC), lateral talocrural (lTC), talonavicular (TN), and posterior subtalar (pST) articular facets around the talus at both visits to map 3D JSW across each. Talocrural joint angulation was measured at each ankle from 3D reconstructions. The t-test was used to determine whether mean angle difference between visits significantly differed from 0°. The dependence of 3D JSW on angle difference and the null hypothesis of no difference in 3D JSW between visits were tested using statistical parametric mapping (SPM). Baseline and follow-up maps were used to give test-retest repeatability using Bland-Altman analysis.

RESULTS: Mean JSW values at visit 1 are shown in the top figure. The difference in angulation between visits was not significantly different from zero (2.7 ± 17.7°, p=0.30). There was a tiny patch of anterolateral mTC joint space that SPM showed to be dependent on joint angulation ($p<0.05$), with ~1 mm of difference in JSW for each degree of difference between visits (middle figure). There was no significant difference in 3D JSW between visits for all joints. Global test-retest bias was 0.0 mm across all joints. Repeatability limits of agreement (sensitivity) at individual joints were: TN ±0.26 mm, mTC ±0.28 mm, pST ±0.34 mm, and lTC joint ±0.40 mm. The optimum sensitivity at each was less than ±0.2 mm in the central joint space (bottom figure).




CONCLUSION: Although there are limits from imaging artefact, if tolerated, then JSM is feasible and sensitive in 3D JSW measurement at least to ±0.2mm at the weightbearing ankle and hindfoot when imaged with cone beam CT.

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**TRANSCATHETER ARTERIAL EMBOLIZATION AS A NOVEL TREATMENT FOR MILD TO MODERATE KNEE OSTEOARTHRITIS: PROTOCOL DESIGN OF A RANDOMIZED SHAM-CONTROLLED CLINICAL TRIAL**

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INTRODUCTION: Transcatheter arterial embolization (TAE) is a novel treatment for knee OA aimed to bridge the treatment gap between conservative and surgical treatment. Angiogenesis and accompanying newly formed nerves are thought to be a contributor to the pain experienced by knee OA patients. This new treatment aims to embolize this neovasculature and subsequently decrease pain symptoms. Initial studies from Japan have shown that TAE is effective in alleviating pain symptoms. However, to eliminate the placebo effect and determine the true efficacy of this treatment a randomized sham-controlled clinical trial is needed.

OBJECTIVES: To assess the efficacy of TAE in reducing pain symptoms in knee OA patients 4 and 12 months after treatment compared to a sham procedure 2) To explore whether TAE and reduction of angiogenesis reduce inflammation and neovasculature in knee OA visualized by (DCE) MRI.

METHODS: 58 patients with mild to moderate (KL 1-3) symptomatic knee OA resistant to conservative therapy will be included and randomized 1:1 either to the intervention or placebo group. In the intervention arm, culprit vessels are identified and catheterized with a microcatheter with micro guidewire. Embozene™ Microspheres 75 µm are used for embolization. Under continuous fluoroscopy and roadmapping the target vessels are embolized until stasis of blood flow. In the sham group patients will be blinded from the operating site by a surgical drape. An incision will be made in the groin after local anesthesia. No catheter will be inserted in the femoral artery. The sham procedure will take approximately 1-2 hours, just like the actual intervention. Outcome measurements will be collected at baseline and 1, 4, 8 and 12 months after intervention. Pain and physical function will be measured using the KOOS questionnaire. MRI will be performed at baseline and after 1 and 4 months. Whole joint assessment will be done using the MRI Osteoarthritis Knee Score (MOAKS). Differential subsampling with Cartesian ordering (DISCO) DCE-MRI will be used to visualize and measure synovitis and angiogenesis using heuristic (i.e. time intensity curves, maximum enhancement etc.) and pharmacokinetic (i.e. $k^{trans}$, *Ve)* parameters. MAGnetic resonance image Compliation (MAGiC) synthetic MRI will be used to obtain T2 relaxation maps of the cartilage. This study protocol was approved by the local ethical committee of the Erasmus medical centre, Rotterdam, the Netherlands.

RESULTS: We have currently included 15 patients and will complete inclusion by the end of 2020. Initial findings (blinded to study arm) of the first 10 patients show a mean KOOS pain score at baseline of 41,1 and 58,8 at 1-month follow-up. This reduction is statistically significant with $p<0.001$ using a paired samples t-test. In the first 10 patients no serious adverse events occurred.

CONCLUSION: TAE constitutes a promising new treatment that may be beneficial patients resistant to conservative therapy. This ongoing clinical trial evaluates the effectiveness of TAE using a randomized sham-controlled study design, and also aims at identifying the working mechanism of TAE using advanced MR imaging techniques.

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DISCLOSURE STATEMENT: No conflict of interest to disclose
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**EVALUATING CHANGES IN BONE PERFUSION AND MINERALIZATION IN RESPONSE TO ACUTE EXERCISE IN AN OSTEOARTHRITIC POPULATION USING HYBRID PET-MR IMAGING**

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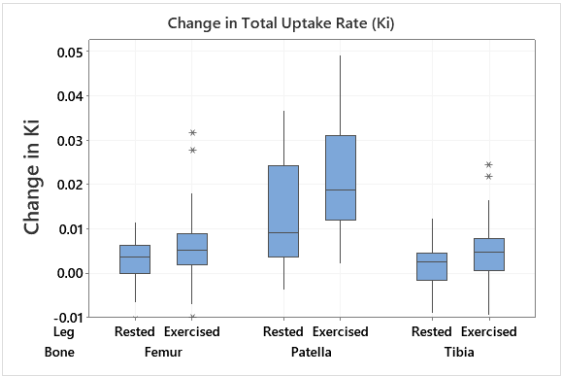
INTRODUCTION: Abnormal bone physiology is a potential mechanism for the development and progression of knee osteoarthritis (OA), a whole-joint disease marked by the development of bone marrow lesions (BML) and osteophytes (OP) and the degeneration of adjacent cartilage. Kinetic modeling of [$^{18}$F]NaF uptake into bone enables quantitative analysis of bone perfusion and metabolism, and has been associated with the presence of structural OA features in the knee. Acute knee loading was shown to alter $^{18}F^-$ kinetic uptake parameters in healthy subjects, suggesting potential utility of this method to study effects of acute loading on metabolic bone response.

OBJECTIVE: We evaluated the response of $^{18}F^-$ kinetic uptake parameters to acute loading induced by a one-legged squat in an OA population with simultaneous PET-MRI imaging.

METHODS: Both knees of 11 subjects with knee OA (59.9±8.2 years; BMI 26.8±5.4; 9 F) were scanned using a 3T whole-body hybrid PET-MRI system under an approved IRB protocol. Subjects were scanned twice on the same day: first at rest, then again after performing a one-legged squat exercise activity to fatigue. For each scan, upon injection of a 2.5 mCi dose of [$^{18}$F]NaF, dynamic PET and bilateral MRI data were obtained over 50 minutes. Dynamic PET data were fit to a two-tissue kinetic model to calculate rates of bone perfusion (K1), tracer extraction fraction (fraction of extravascular $^{18}F^-$ ions binding to the bone matrix) and bone $^{18}F^-$ total uptake rate (Ki = K1*extraction fraction). Kinetic fitting was performed for regions of interest in the patella, tibia and femur. The change in mean SUV (SUVmean), (SUVmax), Ki, K1, and extraction fraction was compared between the rested and exercised legs and regions of interest using a mixed-effects model accounting for clustering within subject and for differences with bone region (alpha = 0.05). MRI Osteoarthritis Knee Score (MOAKS) assessment was performed to compare the change in measures within normal-appearing bone (MOAKS 0) to bone regions with BML or OP (MOAKS score > 0).




RESULTS: Overall SUVmean, SUVmax, Ki, K1, and extraction fraction were significantly different in the femur, patella, and tibia in both legs after the exercise activity ($p < 0.001$ for all). Compared to the rested leg, there was a significant increase in SUVmean, SUVmax, Ki, and K1 in the exercised leg as a result of the exercise ($p < 0.05$ for all uptake parameters). The change in extraction fraction was not significantly different between the exercised and rested legs ($p = 0.490$). The activity-related change in uptake parameters differed by bone region ($p < 0.05$ for all uptake parameters), with the highest change in the subchondral bone of the patella. Furthermore, bone regions with BML had a significantly greater increase in SUVmax ($p = 0.036$), Ki ($p = 0.023$), and K1 ($p = 0.006$) after exercise than normal-appearing bone regions; regions with OP had a significantly greater increase in SUVmax ($p = 0.014$) and K1 ($p = 0.022$).

CONCLUSION: Kinetic parameters of $^{18}F^-$ uptake may be used to study bone response to acute loading in OA.

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**KNEE MECHANICS AND PATIENT REPORTED OUTCOMES CORRELATE TO PATELLOFEMORAL DEEP CARTILAGE UTE-T2* 2 YEARS AFTER ACL RECONSTRUCTION**

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INTRODUCTION: Patellofemoral (PF) joint osteoarthritis (PFOA) is common after ACL reconstruction (ACLR), and high rates of PF cartilage degeneration have been observed within the first 5 years of ACLR. Despite this, associations between altered biomechanics and PF cartilage composition have not been widely examined in this population. Such studies may help to identify modifiable factors to prevent or treat osteoarthritic changes to the PF joint after ACLR.

OBJECTIVES: 1) To test if greater patellar and trochlear deep cartilage matrix disruption, evidenced by higher UTE-T2* values, are related to worse patient reported knee function and pain at 2 years after ACLR. 2) To test if biomechanical changes to the post-ACLR joint, specifically greater external rotation of the tibia, lower knee flexion moment (as a surrogate for lower quadriceps function), and greater knee flexion angle at heel strike, are associated with higher PF cartilage UTE-T2* values.

METHODS: Sixty ACLR subjects at 2 years post-surgery and 20 uninjured controls underwent 3T MRI. UTE-T2* maps were calculated from a series of T2*-weighted images acquired at 8 TEs (32μs -16ms, non-uniform echo spacing) using a radial out 3-D Cones acquisition. Deep articular cartilage (extending from bone-cartilage interface through half the cartilage thickness) was manually segmented in 9mm wide regions centered on patellar and trochlear surfaces. ACLR subjects also completed KOOS questionnaires and walking gait analyses. UTE-T2* means were compared to KOOS scores using Spearman's rho correlations. Side-to-side differences (ACLR limb – contra limb) in external tibial rotation and knee flexion angle at heel strike (ExtRot-HS, KFA-HS) and maximum knee flexion moment (KFM) were compared to UTE-T2* means using Pearson correlations (or Spearman's rho for non-normally distributed data). Effects of graft type, gender, age, BMI, time from injury to surgery and meniscus status were assessed with stepwise linear regression. Bonferroni corrections were applied to adjust for multiple comparisons. UTE-T2* differences between ACLR and control knees were assessed with Mann-Whitney U tests. Gait metric differences between ACLR limbs and single limbs from a separate cohort of 60 age, gender, and BMI-matched historical, healthy controls were assessed with 2-tailed t-tests (or Mann-Whitney U tests).

RESULTS: Greater deep trochlear cartilage UTE-T2* correlated with worse KOOS function in Sports and Recreation and trended toward an increase with worse KOOS Pain (univariate associations: Rho=-0.32, -0.26; $p$=0.015, 0.045). Greater ExtRot-HS and KFA-HS (of the ACLR limb compared to the contra) correlated to higher UTE-T2* values in patellar and trochlear deep cartilages, respectively (univariate associations: R=.40, $p$=0.002; Rho=0.39, $p$=0.002). Greater KFM (ACLR-contra) trended towards higher deep trochlear UTE-T2* (Rho=0.30, $p$=0.019). Stepwise linear regression found no effects of graft type, gender, age, BMI, time from injury to surgery or meniscus status on these results. Patellar cartilage UTE-T2* values, KFA-HS and ExtRot-HS were all elevated in ACLR knees compared to controls ($p$=0.029, 0.001, 0.044).

CONCLUSION: UTE-T2*mapping of patellofemoral joint cartilage provides evidence to support a mechanistic explanation for the development of PFOA after ACLR. Increased external tibial rotation and loss of knee extension likely contribute to patellofemoral cartilage damage and reduced knee function, detectable through an increase in UTE-T2* values in the affected tissues. These findings point to specific surgical and therapeutic targets that may help prevent or reduce patellofemoral joint cartilage degeneration. Furthermore, UTE-T2* mapping of PF cartilage shows utility as a potential outcome metric to assess the effectiveness of candidate interventions to improve patellofemoral health and patient reported outcomes after ACL injury and reconstruction.

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DICLOSURE STATEMENT: none
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**AGREEMENT AND ACCURACY OF FEMOROTIBIAL CARTILAGE MORPHOMETRY IN RADIOGRAPHIC KNEE OA USING DIFFERENT TRAINING SETS FOR AUTOMATED DEEP LEARNING SEGMENTATION – COMPARISON BETWEEN FLASH AND DESS MRI**

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INTRODUCTION: Convolutional neural networks (CNNs) have recently gained strong interest for the segmentation of articular cartilage from MRI. U-Nets are amongst the most widely used CNN architectures. Only few CNN-based methods have reported the accuracy of cartilage morphometry vs manual segmentation, and none have compared various MRI contrasts and orientations.

OBJECTIVE: 1) to examine the performance of automated, U-Net-based cartilage segmentation in knees with radiographic OA (ROA) and its dependence on training data set composition. 2) to compare the performance between two MRI protocols, specifically coronal FLASH with T1-weighted contrast, and sagittal double echo steady state (DESS) with both T1 and T2-weighted contrast.

METHODS: 122 participants with ROA and 92 without symptoms, signs and risk factors of knee OA (the healthy reference cohort (HRC) of the Osteoarthritis Initiative (OAI)) had expert manual segmentation of the femorotibial cartilages, both from coronal FLASH and sagittal DESS 3 Tesla MRI. U-nets were trained from ROA knees (n=86/18 training/validation) and HRC knees (n=50/21). Both the ROA and HRC U-Nets were tested on 18 ROA and 21 HRC knees, respectively (the test set).

RESULTS: Of 122 ROA knees, 35/34/31% were KLG 2/3/4, respectively. In the HRC test set, a mean Dice Similarity Coefficient (DSC) of 0.91 was observed for FLASH, and 0.90 for DESS, both for the HRC- and ROA-trained algorithm. In the ROA test set, DSCs were 0.86/0.86 (FLASH/DESS) for the ROA-trained, and 0.82/0.82 for HRC-trained U-nets. Cartilage thickness computations from automated segmentation in the FLASH test set showed high correlations vs. the manual method. In the HRC test set, results were superior for the HRC U-Net (r=0.96) than for the ROA U-Net (r=0.88), and in the ROA test set, superior for the ROA U-net (r=0.94) than the HRC U-net (r=0.89). The systematic offset for cartilage thickness from automated segmentations was 4.8±4.0% for HRC knees using the HRC U-Net, and 5.8±9.3% using the ROA U-net. It was 11.8±14.4% for the ROA knees using the HRC U-Net) and somewhat smaller (8.8± 11.3%) when using the ROA U-Net. Results for DESS were similar to that observed for FLASH. Offsets in ROA knees were much larger for KLG 4 than for KLG 2 or KLG 3 knees (Fig. 1).

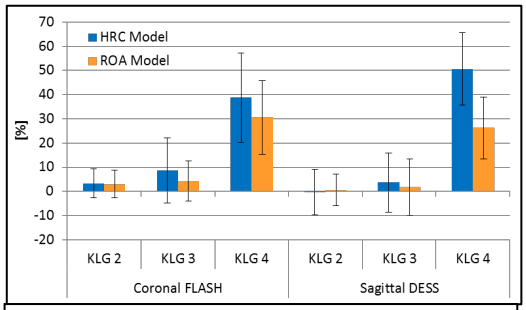


**Fig. 1:** Cartilage thickness offset (automated vs. manual segmentations) stratified by KLG

CONCLUSION: An automated U-net algorithm trained on ROA knees was able to segment and compute cartilage thickness in ROA knees with greater accuracy than one trained on healthy knees, or one trained on a combination of ROA and healthy knees (data not shown). Overestimates of cartilage thickness were large in KLG4 knees. These results were similar for both corFLASH and sagDESS.

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**IS PHYSICAL ACTIVITY ASSESSED WITH ACCELEROMETERS MORE SENSITIVE TO KNEE PAIN THAN CONVENTIONAL FUNCTIONAL PERFORMANCE TESTS? - DATA FROM THE OSTEOARTHRITIS INITIATIVE**

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INTRODUCTION: Functional performance measures (FPMs) represent important instruments in epidemiological and clinical trials of knee OA, as they provide potentially more objective information than patient reported outcomes (PROs). We have shown previously that, amongst different FPMs the Chair Stand Test (CST) is more sensitive to various levels of knee pain than 20m and 400m walk tests.

OBJECTIVE: Given the current interest in the use of wearables for functional evaluations in clinical trials and clinical practice, the aim of this work was to analyze whether physical activity parameters obtained from accelerometry better discriminate between various knee pain strata than the CST.

METHODS: The current analysis was conducted in 552 participants from the Osteoarthritis Initiative (OAI [47% women; age 65±9 years (mean±SD); BMI 28±4]) who had available Numerical Rating Scale (NRS) pain measures for both knees at 48 months follow-up (range 0-10 [low-high]), CST results as well as accelerometer measurements (ActiGraph GT1M uniaxial accelerometers; ActiGraph, Pensacola, FL). Participants with hip pain, or hip or knee joint replacement were excluded from the analysis. Accelerometry parameters included daily counts, minutes of light, moderate and vigorous activity, and moderate/vigorous activity, representing the sum of the latter. Further, bout minutes of moderate/vigorous activity were available, with a bout being defined as an 8 out of 10-minute period with an intensity equal to, or greater than a given threshold. Three thresholds were used for each parameter based on definitions from different authors (Freedson, Swartz, Troiano). Participants were divided into the following strata: no pain (NRS 0), mild (NRS 1/2), moderate (NRS 3/4) or non-acceptable pain (NRS>4) based on the knee with the greater NRS (target knee). Mean values and 95% CIs were calculated for all parameters in each pain stratum. ANCOVA with adjustment for age and BMI was used for statistical analyses, and the Cohen's D as a measure of effect size.

RESULTS: Of the 552 subjects, 44% had no knee pain, 19% mild, 19% moderate, and 18% non-acceptable pain in the target knee. Amongst the accelerometry measures, moderate/vigorous activity as defined by Freedson and Troiano best discriminated between participants with non-acceptable vs. no pain (17.0min [95% CI 13.5, 20.4] vs. 23.7min [21.0, 26.5] and 15.8min [12.5, 19.1] vs. 22.3min [19.7, 25.0] daily activity, respectively (Cohen's D for both =0.33, p-value = 0.001)). Calculating bout minutes of moderate/vigorous activity did not improve the discrimination (Freedson: Cohen's D=0.31, p=0.009; Troiano: Cohen's D=0.30, p=0.011 [ANCOVA]). Daily activity counts and light activity did not reveal significant differences between pain strata. Accelerometer parameters calculated based on thresholds defined by Swartz also did not show significant differences between any of the pain strata. Despite the statistically significant findings, the above accelerometry results did not attain the discriminatory ability of the CST for non-acceptable pain vs. no pain (Cohen's D=0.61, p<0.001). Moreover, the CST - unlike accelerometry - was also able to discriminate between moderate and no pain (Cohen's D = 0.49, p<0.001).

CONCLUSION: Amongst physical activity parameters calculated from accelerometry, moderate/vigorous activity as defined by Freedson and Troiano was most sensitive in discriminating between participants with non-acceptable vs. no knee pain. Yet, accelerometry parameters were not capable of discriminating between different knee pain levels as the CST. Therefore, the CST can be recommended for the use in clinical studies that attempt to monitor improvements in pain and function, with further innovations in accelerometry and its technical analysis being required.

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F. Eckstein is co-owner and CEO of Chondrometrics GmbH; he has consulted for Merck, Bioclinica, Servier, Samumed, Roche, Kolon Tissuegene, Galapagos, Novartis and ICM;
W. Wirth is CTO & co-owner of Chondrometrics GmbH and has consulted for Galapagos.
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**SENSITIVITY OF AUTOMATED CARTILAGE SEGMENTATION IN KLG4 KNEES TO U-NET ARCHITECTURE TRAINING SET COMPOSITION – MODEL SPECIFICITY IS IMPORTANT**

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INTRODUCTION: We have recently reported the agreement and accuracy of automated cartilage segmentation of knees with radiographic OA (compared with healthy ones) using convolutional neural network-based U-Net architecture. We observed that automated cartilage segmentation slightly overestimated cartilage thickness vs. manual segmentation, and that this effect was mainly apparent in KLG4 knees with denuded subchondral bone areas (Wirth et al., same conference).

OBJECTIVE: 1) Examine whether a specific training model of KLG4 knees (n=26) shows better segmentation performance with less cartilage thickness overestimation than a larger, more general model of KLG 2-4 knees (n=86); 2) Explore whether a larger training model of 149 KLG4 knees further improves performance; 3) Compare the relationship between overestimation and denuded areas.

METHODS: The test set included 6 KLG4 knees from the Osteoarthritis Initiative (OAI) who had expert manual segmentation of the femorotibial cartilages, both from corFLASH and sagDESS MRI (Wirth et al. same conference). First, U-nets were trained/validated (n=86/18), using a general ROA model of ROA knees (37% KLG2, 33% KLG3, 30% KLG4). Next, a specific KLG4 model was trained/validated (n=26/6), using only the subset of KLG4 knees with DESS MRI, from the above study. Finally, a larger KLG-specific model was trained/validated in n=125/24 KLG4 knees.

RESULTS: A mean Dice Similarity Coefficient (DSC) across all 4 femorotibial cartilages (TFTJ) of 0.85 was observed for the general (KLG2-4) ROA model using the sagDESS data, the same (0.85) for the small KLG4-specific model, and 0.87 for the larger KLG4-specific model. The average systematic cartilage thickness overestimation by U-net segmentation was 0.24 mm (26%) for the general ROA (KLG2-4) model, 0.16 mm (16%) for the small KLG-4 specific model, and 0.23 mm (24%) for the larger KLG4-specific model. The offsets were largest in the medial femur (cMF: 53%; 43%, and 51%, respectively). The associations (Pearson correlation) between automated and manual cartilage thickness computations were r=0.85, 0.84, and 0.94 for the three models in the TFTJ, and 0.74, 0.87, and 0.92 in the cMF. The dABs involved 22% of the total (TFTJ) subchondral bone area in the test set, 12% in the general ROA training set, 26% in the small KLG4-specific training set, and 24% in the larger KLG4- specific training set. The largest dABs were observed in the cMF (average 56%, vs 33% in the MT, 2%, in the cLF, and 2% in the LT). In the cMF, the correlations between overestimates of cartilage thickness, and the dABs were r= 0.82, 0.95, and 0.92 for the three models, respectively.

CONCLUSION: Overestimates of cartilage thickness by automated U-net segmentation appear to be due to presence of dABs. A small KLG-specific training model using a subset of KLG4 knees only reduced the overestimate of cartilage thickness vs. manual segmentation compared with a more general ROA model (KLG2-4). This specific training model also led to a stronger cartilage thickness correlation of U-net vs. manual analysis, but only in the cMF. The larger KLG4-specific model did not achieve a reduction in the thickness overestimate vs. the general model, but substantially increased the correlation of automated vs. manual cartilage thickness measures in the cMF, and also in the TFTJ. The results suggest that the specificity of the training model is important in automated cartilage analysis.

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**THE INTERPLAY BETWEEN MEDIAL MENISCUS VOLUME AND EXTRUSION; A STRUCTURAL EQUATION MODEL OF OSTEOARTHRITIS DEVELOPMENT**

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INTRODUCTION: Previous research showed that meniscus extrusion and meniscus volume are both independently associated with incidence of knee OA. However, the interplay between these measures remains unclear.

OBJECTIVE: To explore the interplay between (changes in) medial meniscus volume, meniscus extrusion and radiographic knee OA development over 30 months follow-up (FU).

METHODS: Data from the PROOF study were used. This cohort included 407 middle-age women with a body mass index (BMI) ≥27 kg/m$^2$, who were free of knee OA, according to the clinical ACR criteria, at baseline. Demographics were collected by questionnaires. BMI, knee radiographs (for K&L scoring) and knee MR images (for semi-quantitative scoring using MOAKS) were obtained at baseline and FU. Both medial and lateral menisci from all knees at baseline and FU were segmented fully automatically in the coronal, proton-density weighted MRI scan, using in-house developed software. From these, meniscus volumes were calculated. Baseline and FU meniscus body extrusion was quantitatively measured on mid-coronal proton density MR images by one observer (defined as the horizontal distance between outer edge of the meniscal body and the edge of the tibia). Delta-volume and delta-extrusion were calculated by subtracting the baseline value from the FU. By using Structural Equation Modeling (SEM), we developed a theoretical model to assess the interplay between baseline medial central meniscus volume, baseline medial central extrusion, delta medial central meniscus volume, and delta medial central extrusion on the incidence of radiographic knee OA (incident K&L ≥ 2). All estimates were adjusted for confounders (not shown in the figure for clarity reasons), which included BMI at baseline, baseline medial meniscus body width, age, self-reported knee injury, the presence of meniscus pathologies (excluding extrusion) and cartilage defects. BMI change over time and progression medial meniscus tears were only modelled as confounder for estimates between delta meniscus volume, delta extrusion and incident radiographic OA. (IBM SPSS Amos 23.0.0).

RESULTS: The SEM yielded a fair to good fit of the data. The direct effect of both medial meniscus volume and extrusion at baseline on incident OA were statistically significant (Estimate=0.132, p<0.01 and Estimate = 0.210, p<0.01, respectively). Additional indirect effects on incident OA through delta meniscus volume or delta meniscus extrusion were not statistically significant (See figure).

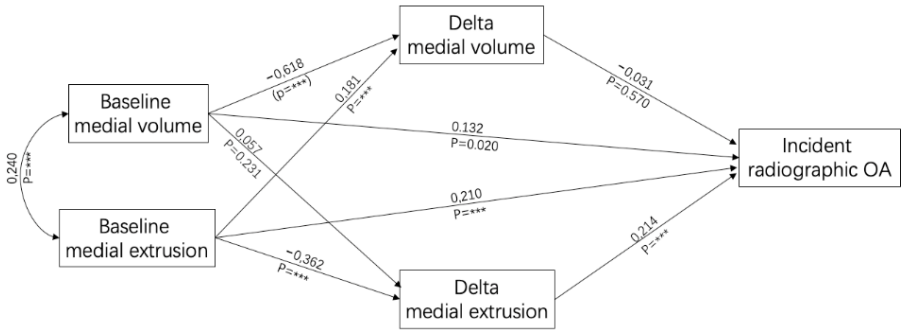


**Figure 1.** Simplified Structural Equation model.

CONCLUSION: Baseline medial meniscus volume and extrusion were independently associated to the incident radiographic knee OA at FU in middle-aged overweight women, while the change in meniscus volume and in extrusion were not involved in these effects. In order to prevent the onset of knee OA, interventions might need to target the onset of meniscal pathologies rather than their progression.

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