3RD INTERNATIONAL OSTEOARTHRITIS IMAGING WORKSHOP

OSTEOARTHRITIS IMAGING:

CAPITALISING ON THE KNOWLEDGE INVESTMENT

3rd International Workshop on Osteoarthritis Imaging

May 13th-16th 2009

Park Inn Hotel

York UK

INDEX

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Osteoarthritis Imaging:

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3rd International Workshop on Osteoarthritis Imaging

May 13th to 16th 2009, York, UK

Organising Committee:

Philip Conaghan	Professor of Musculoskeletal Medicine, University of Leeds, Leeds, UK (Chair)
Felix Eckstein	Director, Institute of Anatomy and Musculoskeletal Research, Paracelsus Medical University, Salzburg, Austria
Mike Bowes	CEO, Imorphics, Manchester UK

Administration:

Helen Livesley	Primary Care Rheumatology Society, North Yorkshire
Begonya Alcacer-Pitarch	Research Fellow, University of Leeds, Leeds UK

Scientific Committee:

Andrew Grainger	Consultant Radiologist, Leeds Teaching Hospitals NHS Trust, Leeds UK
David Hunter	Chief, Division of Research, New England Baptist Hospital, Boston USA
Stefan Lohmander	Professor, Department of Orthopedics, Lund University, Lund Sweden
John Lynch	Director, Imaging Services, San Francisco Coordinating Center, University of California, San Francisco USA
Michael Nevitt	Professor of Epidemiology and Biostatistics, Director OAI Coordinating Center, University of California, San Francisco USA

Rationale

Osteoarthritis (OA) results in a huge burden on individuals and health economies, with the load increasing in an ageing and increasingly obese Western world. Symptomatic therapy often has little effect and there are no generally accepted structure modifying therapies. During the 1990s, there were substantial advances in capabilities of, and access to, modern imaging technologies. In the new millennium, the application of such modern imaging in osteoarthritis clinical research (OA) dramatically increased. While this resulted in improved understanding of the OA phenotype it has created major issues related to understanding and capitalising on the huge amount of rapidly accumulating knowledge in this field.

The primary goals of the proposed workshop are therefore to:

1) provide state of the art review of what we have learned from existing large OA datasets employing modern imaging, as a prelude to formulating research questions for datasets such as the OAI

2) explore the measurement science associated with current quantification of pathological OA features

3) explore the relationship between symptoms and structural abnormalities

4) to assess the current role of imaging biomarkers in cartilage repair, including relationship to clinical features

Structure

The workshop will be composed of several thematic modules, incorporating invited lectures, free papers (selected from abstracts), posters with new data (selected from abstracts) and posters with new perspectives (selected from abstracts). The objective of this structure is to provide ample time for discussion and to focus on current key topics in OA imaging.

Location: Park Inn Hotel, York, UK

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Program

WEDNESDAY 13th MAY

09:30 - 12:30	**Pre-meeting workshop:**	
	Semi-quantitative assessment of OA knee	
Chair:	Philip Conaghan	
09:30 - 09:45	Image acquisition - Frank Roemer, Germany	
09:45 - 10.00	Common OA pathology - Ali Guermazi, USA	
10:00 - 10:30	Group exercise I	
10:30 - 11:00	Break	
11:00 - 12:00	Whole organ scoring methods - Ali Guermazi/Frank Roemer	
12:00 - 12:30	Group exercise II	

Participants will gain an understanding of common OA MRI pathologies and understand common semi-quantitative assessments of these pathologies.

12:30 Registration and lunch

14:00 - 14:15 **Welcome -** Philip Conaghan

14:15 - 16:00 **OA Imaging State of the Art Session: where are we now on assessing progression?**

Chair: Philip Conaghan

Sample guiding question: What have we learnt from recent large OA studies about structural progression?

14:15 - 14:45	Mike Nevitt, USA	Conventional radiographs
14:45 - 15:15	Felix Eckstein, Austria	MRI: Cartilage
15:15 - 16:00	David Hunter, USA	MRI: Non-cartilage features

16:00 - 16:30 Break

16:30 - 18:10 **Abstract Oral Presentations: Session 1**

Chair: Mike Nevitt

Nº 010- Which subchondral bone measure is the best predictor of cartilage damage?
Dore D., Quinn S., Ding C., Jones G.

Nº 004- A canonical set of morphological measures for articular cartilage in the healthy and diseased human knee.
Buck RJ, Wyman BT, Hellio Le Graverand M-P, Wirth W, and Eckstein F

Nº 014- Effects of weight loss on articular cartilage proteogylcan content utilizing dGEMRIC at 3T.
Anandacoomarasamy A., Caterson I., Smith G., Leibman S., Giuffre B., Fransen M., Sambrook P., March L.

Nº 007- Comparative study of longitudinal cartilage change using coronal flash, sagittal DESS, and coronal MPR DESS- data from the OA initiative
Wirth W, Nevitt M, Hellio Le Graverand M-P, Benichou O, Dreher D, Davies R.Y, Lee J, Picha K, Hudelmaier M, Eckstein F for the OAI investigators

Nº 032- Do baseline synovitis and effusion predict structural progression in subjects with early or pre-OA? – the MOST study
Roemer F.W., Guermazi A., Felson D.T., Niu J., Nevitt M.C., Crema M.D.,Lynch J.A., Lewis C.E., Torner J., Zhang Y.

Evening Events

19:00 Buffet dinner in the Henley Suite, Park Inn Hotel

20:10 Meet in hotel foyer for Ghost Walk

THURSDAY 14th MAY

09:00 - 10:40	**Novel imaging modalities in OA: what can they measure?**	
Chair:	Felix Eckstein	

Sample guiding question: What do we know about the pathology visualised and measurement properties with other imaging modalities and newer applications of MRI?

09:00 - 09:25	Richard Wakefield, UK	Ultrasonography
09:25 - 09:50	Bernie Dardzinski, USA	Where are we with molecular imaging?
09:50 - 10:15	Tony Redmond, UK	Visualising function
10:15 - 10:40	Charles Mamisch, Switzerland	Measuring cartilage repair

10:40 - 11:00	Break
11:00 - 12:30	**Poster viewing**
12:30 - 14:00	Lunch (with thanks to our Gold Sponsor, **Novartis**)

14:00 - 16:00	**MR Imaging biomarkers: what happens to them?**	
Chair:	David Hunter	

Sample guiding question: What do we know about changes in biomarkers from their earliest detection to later disease?

14:00 - 14:30	Frank Roemer, USA	Bone marrow lesions
14:30 - 15:00	Graeme Jones, AUS	Cartilage defects
15:00 - 15:30	Ali Guermazi, USA	Synovium
15:30 - 16:00	Mike Bowes, UK	Bony morphological features

16:00 - 16:30	Break

16:30 - 18:10 **Abstract Oral Presentations: Session 2**

Chair: Andrew Grainger

Nº 009- The BM lesion of OA: is less fat more relevant than more water?
Simkin P.A.

Nº 001- Presence, size and location of denuded areas of subchondral bone in the knee as a function of radiographic stage-data from the OA initiative.
Frobell RB, Wirth W, Wyman B, Benichou O, Dreher D, Davies R.Y, Nevitt M, Lee J, Baribaud F, Hudelmaier M, Eckstein F for the OAI investigators.

Nº 027- Active appearance modelling of the knee using DXA images
Aspden, R.M., Gregory, J.S., Barr, R.J., Yoshida, K., Gilbert, F.J., Alesci, S., Lee, J.H., Reid, D.M.

Nº 023- Delayed gadolinium enhanced MRI of meniscus: differences in OA
Li W, Edelman RR, and Prasad PV

Nº 041- Comparison of WORMS and BLOKS semi-quantitative knee MRI scoring for assessing cartilage loss: results from the osteoarthritis initiative**.**
Lynch J.A, Roemer F.W., Felson D.T., Guermazi A., Nui J., Maeda J., Nevitt M.C.

Free Evening

For those wanting to eat at the Park Inn, there will be a hotel BBQ served in the restaurant from 18:30 - 20:30 hrs with admittance by ticket only – please see our conference reception desk for free tickets if you are interested.

FRIDAY 15th MAY

09:00 - 10:30 **Challenges and models for trials of structure modification**

Chair: Stefan Lohmander

Sample guiding question: What are the challenges for drug trials of structure modification and are there models other than the knee?

09:00 - 09:30	Peter Mitchell, USA	Current overview of structure modification drug development
09:30 - 10:00	Jennifer Lee, USA	The path to structure modification: connecting the dots from pre-clinical to clinical studies
10:00 - 10:30	Charles Mamisch, Switzerland	Is the knee the only human model?

10:30 - 11:00 Break

11:00 - 12:20 **Abstract Oral Presentations: Session 3**

Chair: Graeme Jones

Nº 038- Joint distraction as treatment of end stage osteoarthritis leads within one year to structural cartilage repair as evaluated by MRI and X-ray
Lafeber FPJG., Cotofana S., F. Intema F., VanRoermund PM., Eckstein F., Marijnissen ACA.

Nº 002- Two year longitudinal development of post traumatic bone marrow lesions in the acutely ACL injured knee
Frobell RB, Hellio-LeGraverand MP, Roos HP, Roos EM, Lohmander LS

Nº 013- Same day T1□, T2 and dGEMRIC measures of cartilage post- ACL injury
Pedersen D.R., Tadimalla S., Thedens D.R.,Martin J.A.,Amendola A.

Nº 035- Cartilage-Bone Contrast Behavior in OAI Progression Sub-cohort; Correlation to WOMAC Scores
Totterman S, Tamez-Peña J, Schreyer E, González P, Hunter D

12:20 - 14:00 Lunch (with thanks to our Gold Sponsor, **Merck Serono**)

14:00 - 15:30	**Capitalising on the Osteoarthritis Initiative**	
Chair:	Gayle Lester	

Sample guiding question: How can we capitalise on the OAI in light of what we've learnt from other cohorts?

14:00 - 14:15	Mike Nevitt, USA	Overview of data now available from OAI
14:15 - 14:30	John Lynch, USA	What have researchers done with OAI images so far?
14:30 - 14:45	Gayle Lester, USA	Research priorities and opportunities

14:45 - 15:30 Break outs

4 break out groups – led by Nevitt, Lynch, Lester, Lohmander

Each group to determine their top 5 priority research areas for OAI

15:30 - 16:00 Feedback from the 4 break out groups

16:00 - 17:30 Concluding round table discussion

Evening Events

18:45 Meet in hotel foyer for walk to the National Railway Museum for wine reception in the Great Hall - housing a stunning display of some of the NRM's finest locomotives, including Mallard, Eurostar and the Bullet Train - followed by dinner on the platform of Station Hall where you will dine amidst luxurious carriages and historic locomotives set against the backdrop of a period station.

SATURDAY 16th MAY

Post conference event

Bus pick up outside hotel at 0915 for trip to Harewood House, which is home to the Earl of Harewood, the Queen's cousin. The home is one of the best kept stately homes in Europe with sections open to the public. It is situated in magnificent landscaped gardens.

The visit will include entry to the house and a private guided tour, followed by lunch (included). There will be ample time for seeing the gardens and walks.

The bus will leave Harewood House at 1500 to return to the hotel.

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Abstracts

PRESENCE, SIZE AND LOCATION OF DENUDED AREAS OF SUBCHONDRAL BONE IN THE KNEE AS A FUNCTION OF RADIOGRAPHIC STAGE - DATA FROM THE OA INITIATIVE

[1]Frobell RB, [2]Wirth W, [3]Wyman B, [4]Benichou O, [5]Dreher D, [6]Davies R.Y, [7]Nevitt M, [8]Lee J, [9]Baribaud F, [1,2]Hudelmaier M, [1,2]Eckstein F for the OAI investigators
[1]Paracelsus Medical University, Salzburg, Austria; [2]Chondrometrics GmbH, Ainring, Germany, [3]Pfizer, New London, CT, [4]Eli Lilly & Co, Indianapolis, IN;[5]Merck Serono SA, Geneva, Switzerland; [6]Glaxo Smith Kline, Collegeville, PA; [7]UCSF, San Francisco, CA; [8]Wyeth Research, Collegeville, PA [9]Centocor, Radnor, PA

INTRODUCTION: Denuded areas of subchondral bone (dAB) were recently shown to be associated with the presence and incidence of pain, and with the rate of cartilage loss in longitudinal studies of knee OA. Little, however, is known about the presence and size of dABs in women and men with different radiographic stages of OA, and where they are typically located within the knee.
OBJECTIVE: To investigate the presence, size, and location of dABs within the femorotibial (FT) cartilage plate of knees with different KL and JSN grades, using MRI and quantitative cartilage analysis.
METHODS: A subsample of the OAI (public-use data sets 0.2.1 [clinical] and 0.C.1 [image data]) was studied cross-sectionally (n=537, age 62.1, SD 9.7 years). All participants had ROA in at least one knee; a simulated KL grade and JSN grades were based on the OAI clinic readings (OAI public database). Segmentation of the total area of subchondral bone (tAB) and cartilage surface (AC) of the FT cartilage plates (MT, LT, cMF, cLF) was performed using the coronal FLASHwe acquisitions of the right knee at baseline. The dAB was defined as the tAB not covered by AC and was reported as % of the tAB denuded.

RESULTS: Few KLG 0-1 knees, but most of the KLG4 knees displayed dABs (Table 1). In total, 40% of the knees had at least one dAB (29% of the KLG2 and 49% of the KLG3 knees; 33% of the female and 50% of the male knees). In knees with dAB, the location was exclusively in the medial compartment in 28%, only in the lateral compartment in 44%, and bicompartmental in 28% of the knees. The LT was most commonly affected, but the presence of dAB was relatively similar amongst the plates (Table 1). The presence and size of the dABs increased with greater KL grades (P<0.001, Spearman r=0.440). Presence of medial and bi-compartmental (P<0.001), but not that of lateral dABs (p=0.52) was significantly related to simulated KL grades. Presence of medial dABs was significantly associated with medial (P<0.001), but not with lateral JSN. Presence of lateral and bi-compartmental dABs was significantly associated with lateral and medial JSN (P<0.017)

Table 1: Presence (n and % of sample) and size (%dAB, of those with dAB) in FT cartilage plates

Simulated KL grade		Men				Women			
		MT	cMF	LT	cLF	MT	cMF	LT	cLF
KL 0 -1			n=26				n=15		
(No or possible	n (%)	4 (15)	2 (8)	2 (8)	2 (8)	0	1 (7)	1 (7)	1 (7)
osteophytes)	% dAB (median)	4.7	3.5	3.2	7.5	-	2.1	7.4	1.5
KL 2			n=86				n=153		
(definite osteophyte)	n (%)	4 (5)	8 (9)	13 (15)	16 (19)	8 (5)	7 (5)	13 (9)	19 (12)
	% dAB (median)	2.3	8.4	4.3	4.6	2.2	3.5	3.0	4.7
KL 3			n=86				n=149		
(osteophytes and	n (%)	23 (27)	18 (21)	26 (30)	16 (19)	25 (17)	24 (16)	35 (24)	19 (13)
mild-modearate	% dAB	4.3	5.6	4.3	4.5	4.1	7.7	6.6	5.2
JSN)	(median)								
KL 4			n=13				n=9		
(osteophytes and	n (%)	12 (92)	10 (77)	8 (62)	3 (23)	4 (44)	6 (77)	4 (44)	2 (22)
severe JSN)	% dAB (median)	19.4	41.4	6.4	15.8	12.1	17.9	9.0	11.7
All			N=211				N=326		
	n (%)	43 (20)	38 (18)	49 (23)	37 (18)	37 (11)	38 (12)	53 (16)	41 (13)
	% dAB (median)	6.2	7.9	4.9	5.3	4.2	7.7	6.0	5.2

CONCLUSION: A strong relationship between the presence of dAB and KL grade was observed. A surprisingly large number of participants displayed lateral femorotibial dABs, most commonly in LT. Medial dABs were associated with greater simulated KL grades and medial JSN, whereas lateral compartment dABs were associated with lateral and medial JSN, but not with KL grades. Bicompartmental dABs were associated with simulated KL grades, and both medial and lateral JSN.

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DISCLOSURES: see affiliations. ACKNOWLEDGMENT: We thank the Chondrometrics readers and the OAI investigators.
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TWO YEAR LONGITUDINAL DEVELOPMENT OF POST TRAUMATIC BONE MARROW LESIONS IN THE ACUTELY ACL INJURED KNEE

RB Frobell[1,2], MP Hellio-LeGraverand[3], HP Roos[1], EM Roos[1,4], LS Lohmander[1]

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INTRODUCTION: Trauma to the knee is a risk factor for OA development. Post traumatic bone marrow lesions (BML) are seen in almost all of the MR images in the acute phase of anterior cruciate ligament (ACL) injury. The development of BMLs over time and their relation to OA is not known.

OBJECTIVE: To investigate longitudinal 2 year development of post traumatic BML following ACL injury and ACL reconstruction using MRI morphometry on this development.

METHODS: We prospectively followed a sub-sample of an ongoing randomized controlled trial (the KANON-study), 61 subjects (mean age 26 years, 16 women) with an acute ACL rupture in a previously un-injured knee using a 1.5T MR magnet at baseline (< 5 weeks from injury), 3, 6, 12 and 24 months. 34 had an early ACL reconstruction (median of 44.5 days from injury), 11 had a late ACL reconstruction (median of 408 days from injury) and 16 were treated with rehabilitation alone. BML data were obtained from state-of-the-art automatic computer assisted segmentation of MR images and was regionalized as: Medial / lateral tibia (MT/LT), femur (MF/LF) and Patella (P).

RESULTS: At baseline, all knees (100%) had BML in at least one region of the knee (total mean volume 25.9 ml, SD 16.5). After two years BMLs of the knee had resolved entirely in 28 (46%) knees and the mean BML volume had decreased to 1.5 (SD 3.9) ml (95% decrease). The main decrease of BML volume occurred within the first 3 months (Table 1). 11/22 knees with total resolution of their BMLs at 12 months developed new BML during the second year. A late ACL reconstruction was related to larger BML volumes in LF (P=0.009) and P (P=0.008) at 24 months compared to early ACL reconstruction and rehabilitation alone. There were no significant differences between those treated with an early ACL reconstruction and those treated with rehabilitation alone with regard to the presence of BML in any region at 24 months (P>0.055).

Table 1. The number of knees affected by BML and mean BML volume over 24 months (N=61).

	LF	LT	MF	MT	P
Baseline, N (%)	47 (77)	58 (95)	34 (56)	54 (89)	7 (12)
Volume, ml (SD)	6.9 (6.3	12.9 (7.8)	2.2 (3.9)	8.0 (7.7)	0.3 (0.7)
3 months, N (%)	36 (59)	44 (72)	24 (39)	40 (66)	8 (13)
Volume, ml (SD)	4.2 (4.8)	5.0 (4.6)	2.2 (3.1)	3.9 (3.7)	1.4 (1.4)
6 months, N (%)	24 (39)	38 (63)	19 (31)	38 (63)	12 (20)
Volume, ml (SD)	3.5 (3.2)	3.8 (2.8)	1.4 (1.6)	3.4 (3.5)	1.5 (1.1)
12 months, N (%)	14 (23)	16 (26)	13 (21)	20 (33)	16 (26)
Volume, ml (SD)	3.9 (4.9)	3.0 (2.7)	3.1 (7.3)	3.8 (5.8)	0.8 (0.9)
24 months, N (%)	9 (15)	16 (26)	4 (7)	15 (25)	8 (13)
Volume, ml (SD)	1.2 (1.7)	2.7 (4.0)	0.1 (0.1)	2.2 (2.6)	0.3 (0.5)

CONCLUSION: These results confirm previous findings of a gradual resolution of post traumatic BML following ACL injury. However, large individual variations were found and, interestingly, 50% of the knees developed new BML during the second year after injury. An early ACL reconstruction did not protect against a presence of BML at 24 months as compared to rehabilitation alone, suggesting that increased mechanical stability at rest is not sufficient to prevent the development of post traumatic BMLs 2 years after injury.

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Nº 003 DIFFERENCES IN QUANTITATIVE MR IMAGING OF CARTILAGE MORPHOLOGY BETWEEN SAGITTAL VERSUS CORONAL ACCQUISITIONS OF THE FEMOROTIBIAL JOINT

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INTRODUCTION: Sagittal 1.5mm SPGR/FLASH sequences are a common standard in morphometric cartilage imaging. They have the advantage of covering all cartilage plates in the femoropatellar and femorotibial (FT) compartment, including the posterior aspects of the femoral condyles. Coronal acquisitions with thinner slices (1.0mm) have been advocated for optimal delineation of the cartilage in the weight-bearing FT compartment, because of the smaller partial volume effects in the internal and external aspects of the tibia and femoral condyles.

OBJECTIVE: To directly compare the rate and sensitivity to change in cartilage morphology between 1.0 mm coronal vs. 1.5 mm sagittal acquisitions (FLASHwe @ 3 Tesla) over 2 years in knees with radiographic OA.

METHODS: A subsample of 55 participants with definite medial radiographic OA (29 KLG2, 26 KLG3) from a larger study (A9001140) was analyzed. 1.0mm coronal and 1.5mm sagittal FLASHwe MR images were acquired at 7 centres, at baseline and at 24 months. The images were processed by 7 experienced readers. Segmentation of the medial (MT) and lateral tibial (LT), and the medial (cMF) and lateral weight-bearing femoral condyle (cLF) was performed in the coronal and sagittal images pairs, with blinding to the order of acquisition. Coronal and sagittal pairs were processed by the same reader, and segmentations were quality controlled by one person (F.E.). Cartilage thickness over the entire subchondral bone area (ThCtAB) was computed in 5 subregions of the medial and lateral tibia, and in 3 subregions of the medial and lateral weight bearing femur, using custom software.

RESULTS: Only small changes were observed in the lateral FT compartment. Results for the medial FT com-partment are shown in Table 1: In MT, the mean change (MC%) and standardized response mean (SRM = MC/SD of change) was similar between coronal and sagittal images, but in cMF it was higher for the sagittal scans, also in external and internal subregions (ecMF, icMF). Only in iMT, the SRM for coronal (-0.24) was greater than for sagittal images (-0.10). The longitudinal changes were moderately correlated between coronal and sagittal scans, with the highest agreement in eMT and ccMF. The pattern of cartilage loss (relationship between subregions) was similar for coronal and sagittal scans.

Table 1: Mean change (MC%), standardized response mean (SRM) in cartilage thickness (ThCtAB) over 24 months; p values for Y2 versus BL measurement. Correlations (r) are given as Pearson and Spearman rho.

	1.0 mm coronal			**1.5 mm sagittal**			**Correlation**	
	MC%	SRM	p	MC%	SRM	p	Pearson	Spearman
MT	-1.7	-0.41	0.004	-1.9	-0.38	0.007	0.23	0.28
cMT	-2.7	-0.42	0.003	-2.8	-0.41	0.004	0.20	0.15
eMT	-4.0	-0.41	0.004	-4.7	-0.39	0.006	0.65	0.37
iMT	-1.0	-0.24	0.079	-0.8	-0.10	0.47	0.12	0.13
aMT	-1.3	-0.21	0.12	-0.7	-0.10	0.45	0.24	0.21
pMT	-0.1	-0.04	0.79	-1.2	-0.15	0.28	0.05	0.18
cMF	-1.4	-0.16	0.23	-2.3	-0.36	0.010	0.40	0.20
ccMF	-2.3	-0.20	0.14	-3.5	-0.31	0.025	0.52	0.30
ecMF	-2.0	-0.15	0.28	-1.9	-0.30	0.029	0.27	0.30
icMF	-0.2	-0.04	0.76	-1.5	-0.20	0.15	0.21	0.13

c = central, e =external, i =internal, a = anterior, p =posterior subregion,

CONCLUSION: Surprisingly, the 1.5mm sagittal images displayed a similar rate and sensitivity to change in cartilage thickness over 2 years in MT, and a greater rate and sensitivity in cMF than 1.0mm coronal images. Although partial volume effects are stronger in internal and external subregions in sagittal (and in anterior and posterior subregions in coronal) scans, the spatial pattern of cartilage loss was similar between both orientations.

SPONSOR: Pfizer Global Research and Development (PGRD). DISCLOSURE STATEMENT: see affiliations. ACKNOWLEDGEMENT: A9001140 investigators and technicians, and Chondrometrics technicians.CORRESPONDENCE ADRESS: dr-susanne-maschek@web.de

A CANONICAL SET OF MORPHOLOGICAL MEASURES FOR ARTICULAR CARTILAGE IN THE HEALTHY AND DISEASED HUMAN KNEE

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INTRODUCTION: In the study of osteoarthritis and other joint diseases, morphological measures of cartilage are frequently obtained to assess disease status or progression. An international group of experts recommended definitions and nomenclature for MRI based measures of cartilage morphology, and these include cartilage volume (VC), measures of surface area (tAB, AC, cAB,dABp) and measures of mean cartilage thickness (ThCtAB.Me, ThCcAB.Me,VCtAB = VC divided by tAB). These measurements can be taken on several knee surfaces (e.g. patella, medial tibia, lateral tibia, femur and specific regions of the femur), creating a large set of measurements available for examination and statistical testing in a given study. As many of these morphological measures are strongly related, some may be redundant or contain minimal additional information.

OBJECTIVE: Examine the relationship of common morphological measurements of knee cartilage to determine whether a subset of measurements can fully and accurately reflect differences in any or all measurements, both in cross-sectional and longitudinal studies.

METHODS: 152 female participants were followed over 2 years at 7 clinical centers using 3T MR imaging (1.0 mm coronal FLASHwe). 77 participants had no evidence of radiographic OA in either AP or Lyon Schuss radiographs, whereas 75 displayed medial femorotibial radiographic OA in either AP or Lyon Schuss radiographs. Segmentation of the medial and lateral femorotibial cartilages (MT, LT, cMF, and cLF) was performed using custom software (Chondrometrics). Knee cartilage measurements included cartilage volume (VC), several surface measures (cAB, tAB, AC, pct.dAB), two mean thickness measures (ThCcAB.aMe, ThCtAB.aMe) and VC adjusted for tAB (VCtAB). Coefficient of determination, R^2, and standard linear regression models were used to assess statistical relationships between the various measures. Analysis of variance (ANOVA) was used for variance decomposition of VC.

RESULTS: The 5 measures, ThCcAB.aMe, ThCtAB.aMe, cAB, tAB, and pct.dAB, have known mathematical relationships and may be reduced to a canonical group of three measures without loss of information: (ThC*AB.aMe, *AB, pct.dAB), with * representing either t or c. The relationship between either ThC*AB.aMe and *AB is not mathematically defined, but the R^2 was < 25% over all plates both cross-sectionally and longitudinally, so the two measures had little overlap in information.

Table 1 provides the range of R^2 comparing two measures of knee cartilage (identified as Response and Predictor) across the 4 femorotibial cartilage plates for both cross-sectional and longitudinal studies. The percent difference between VCtAB and ThCtAB.aMe was between 1% and 9% across all plates for baseline and <1% for longitudinal analysis.

Table 1

Response	Predictor	X-Section	Longitudinal
AC	cAB	> 91%	58 - 85%
VCtAB	ThCtAB.aMe	> 98%	> 95%
VC	ThCcAB.aMe	66% - 76%	74% - 90%
VC	tAB	43% - 65%	9% - 43%
VC	ThCcAB.aMe + tAB	98% - 99%	87% - 97%

CONCLUSION: This study shows that the following measures of cartilage morphology: total area of subchondral bone (tAB), percent denuded area of the subchondral bone (pct.dAB), and mean cartilage thickness over the tAB (ThCtAB.aMe) explain nearly all variation in common cartilage morphology measures observed in cross-sectional or longitudinal studies, both in healthy and in osteoarthritis knees. Hence these three measures may be considered a canonical set for describing structural change in cartilage in OA.

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DISCLOSURE STATEMENT: see affiliations
ACKNOWLEDGMENT: the A9001140 investigators and technicians, and the Chondrometrics readers
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EFFECTS OF EXERCISE INTERVENTION ON KNEE MORPHOLOGY IN MIDDLE-AGED WOMEN: A LONGITUDINAL ANALYSIS USING MR IMAGING

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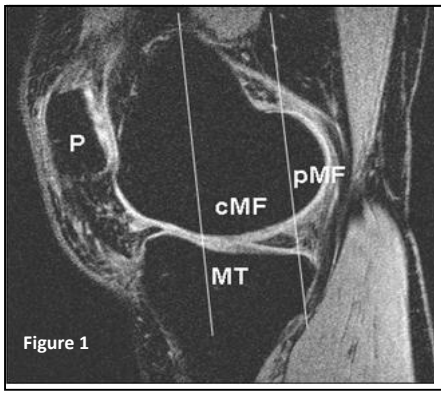
INTRODUCTION: Epidemiological studies showed a positive relationship between physical activity and cartilage volume and have suggested that exercise may protect against osteoarthritis. Cross-sectional experimental studies have, however, failed to show significant differences in knee cartilage morphology between athletes and non-athletic controls.

OBJECTIVE: To test the hypothesis that knee cartilage morphology, specifically regional cartilage thickness and global subchondral bone area, is modified in sedentary, untrained adult women who increased their physical fitness during a 3-month supervised exercise intervention.

METHODS: 38 untrained women, aged 45-55 years, were randomly assigned to: endurance training (ET=18), strength training (ST=15), autogenic training (control group, AT=5). Patellar and (subregional) femorotibial knee cartilage morphology was determined quantitatively from sagittal MR images after segmentation, using custom software (Chondrometrics Works) before and after the 3 month supervised training intervention (Fig. 1).



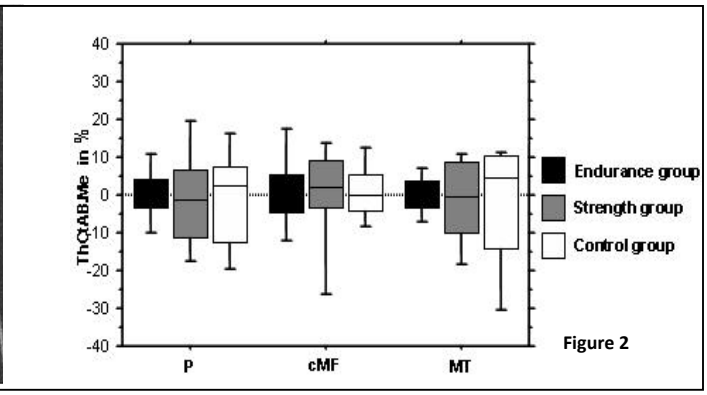


Figure 1: Sagittal MR image acquired with a sagittal fat suppressed T1 weighted spoiled gradient echo sequence: P = patella, MT = medial tibia, cMF = central medial femur, pMF = posterior medial femur.

Figure 2: Percent difference and standard deviation in mean cartilage thickness (ThCtAB.Me) of the patella (P), central medial femur (cMF) and medial tibia (MT) before and after exercise intervention for the different training groups: ET, ST, AT. No significant differences were found in any of the investigated cartilage plates.

RESULTS: Whereas the ET group showed a significant increase in cardio-respiratory fitness (VO_2 max) and the ST group a significant increase in the maximal voluntary isometric contraction (MVIC) force of the leg, MRI data did not show significant differences in knee cartilage thickness (Fig. 2), cartilage volume, subchondral bone area, or regional cartilage thickness between baseline and follow-up acquisitions within any intervention group.

CONCLUSION: Albeit the participants displayed significant increases in physiological performance parameters and in thigh muscle cross sectional areas (Hudelmaier et al.: same conference), this randomized longitudinal study provides no evidence that a 3 month exercise intervention in untrained middle aged women can significantly alter knee cartilage morphology. Longitudinal evidence supporting that a training program can induce functional adaptation of articular tissues and may protect against knee osteoarthritis remains to be presented.

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EFFECT OF EXERCISE INTERVENTION ON THIGH MUSCLE VOLUME AND ANATOMICAL CROSS SECTIONAL AREAS – QUANTITATIVE ASSESSMENT USING MRI

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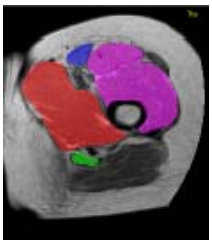
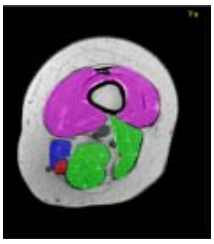
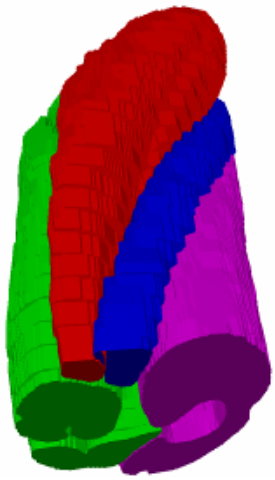
INTRODUCTION: It has been shown that moderate muscle training of the quadriceps positively affects knee pain and physical function in knee OA and may also protect against cartilage loss. Strength training is known to increase the maximal muscle force, which was shown to be correlated with the (physiological) muscle cross sectional area (PCSA). However, it is currently not known at which anatomical level (proximal/ distal length) of the quadriceps and other thigh muscles, is most suitable for monitoring training effects.

OBJECTIVE: To test the hypothesis that a) the effect of a 3-month supervised exercise intervention (strength, endurance, and autogenic [control] training, respectively) in sedentary, untrained adult women can be monitored quantitatively by assessing thigh muscle volumes using MRI, and b) to determine at which proximal-to-distal anatomical level the increase in the anatomical CSA is most pronounced.

METHODS: 41 untrained peri-menopausal women, aged 45-55 years, were randomly assigned to three groups: endurance training (ET=19), strength training (ST=16), and autogenic training (AT=6). The leg muscles were exercised exclusively in ET (cycling) and ST by a supervised training performed 3 times per week for 60 min. over a period of 12 weeks. During the same period AT met once a week for 60min and exercised dominantly the upper body. MRIs of the thigh were acquired before and after the training intervention period on a 1.5 Tesla magnet (NT intera, Philips Medical Systems, Netherlands), employing a T1 weighted Turbo Spin Echo (TSE) sequence (TR=1541ms, TE=15ms, FA=90°, section thickness=10mm, in-plane resolution=0.78mm², acquisition time=1.57min). A region of interest (ROI) was defined between the femoral neck proximally (Fig. 1 top left) and the rectus femoris tendon distally (Fig. 1 bottom left), in which the extensors (quadriceps = magenta)), flexors (green), adductors (red) and sartorius (blue) were segmented manually (Fig. 1). Muscle volumes were determined by numerical integration of the segmented voxels, and the anatomical CSA derived from the 3D reconstruction (Fig. 1, right) at 10% intervals (proximal to distal) throughout the ROI.







RESULTS: At baseline, the correlation between muscle volume and mean CSA (all levels averaged) ranged from r=0.89 for the extensors to r=0.95 for the adductors. With strength training, the volume and mean CSA of the quadriceps increased by 3.1% (standardized response mean [SRM] = 1.3, p<0.0001), that of the flexors by 3.5% (SRM 0.9; p<0.01), that of the adductors by 3.9% (SRM 1.2; p<0.0001). The largest increases were seen at the 30% level from proximal to distal (5.3%, 9.2%, and 5.6%, respectively) and only small increases and SRMs were seen in the distal half of the muscles. With ET, the volume and mean CSA of the quadriceps increased by 3.8% (SRM = 1.4, p<0.01), the greatest effect being at the 20% and 30% level. No significant effect was observed in the flexors and adductors in the ET group, and no effect in any muscle in the controls.

CONCLUSION: The results show that the effect of exercise intervention can be quantitatively monitored using MRI-based muscle volumetry. Measurement of anatomical CSA at a 30% level between the femoral neck and the rectus femoris tendon can most effectively demonstrate exercise-based changes in all muscle groups, whereas changes in the distal half of the thigh are much less pronounced

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COMPARATIVE STUDY OF LONGITUDINAL CARTILAGE CHANGE USING CORONAL FLASH, SAGITTAL DESS, AND CORONAL MPR DESS - DATA FROM THE OA INITIATIVE

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INTRODUCTION: Quantitative analysis of knee cartilage morphology with MRI using FLASH was found accurate, reproducible, and sensitive to change in OA, but FLASH requires relatively long acquisition times. Double echo steady state (DESS) imaging permits acquisition of thin, near-isotropic sagittal images covering all knee cartilage plates in <10 minutes, but the greater number of slices increases analysis time and cost. Both sequences are part of the OA Initiative (OAI) imaging protocol.
OBJECTIVE: 1) To compare the rate of and sensitivity to change of cartilage loss in OA between FLASH and DESS, 2) to determine the correlation of changes between FLASH and DESS, and 3) to study how segmentation of only every 2nd slice of the DESS affects the sensitivity to change.

METHODS: A subsample of the OAI (public-use data set versions 0.1.1[clinical] 0.C.1 and 1.C.1 [image data]) was studied (n=80, age 60.6 y., SD 9.1 y., 32 men, 48 women). We used baseline and 1 year follow up acquisitions of the right knee with the coronal (COR) FLASH (1.5 x 0.31 x 0.31mm), the sagittal (SAG) DESS (0.7x 0.37 x 0.46 mm) and a coronal multiplanar reconstruction (MPR) of the DESS (1.5 x 0.37 x 0.37 mm). Segmentation of the medial tibia (MT) and medial weight-bearing femur (cMF) was performed by experienced readers. Longitudinal change in cartilage thickness (ThCtAB) over 1 year was measured in MT, cMF, the medial femorotibial compartment (MFTC = MT+cMF) and in central subregions of these plates (cMT, ccMF, cMFTC) using COR FLASH, SAG DESS, every 2nd slice of the SAG DESS (odd and even, respectively) and COR MPR DESS.

RESULTS: In MFTC, cMFTC, cMF and ccMF, the mean reduction over one year (MC%) tended to be greater for the SAG DESS and COR MPR DESS than for COR FLASH, while the standardized response mean (SRM) was similar between the 3 protocols (Table 1). In MT, the SRM for corFLASH was lower than for SAG or COR MPR DESS. The baseline values (ThCtAB) displayed high correlations (Pearson) of r ≥ 0.90 between COR FLASH, SAG DESS (all slices) and COR MPR DESS. The correlation of the 1 year changes between the 3 protocols ranged from r= 0.51 to 0.90 (Pearson) and from 0.28 to 0.64 (Spearman rho) for the plates/subregions given in Table 1. Using every 2nd slice of the SAG DESS (odd or even slices) did not reduce the MC% and SRM (Table 1).

Table 1: Mean change in percent (MC%) and standardized response mean (SRM) for cartilage thickness (ThCtAB) in the medial femorotibial compartment (MFTC) over 1 year: *p<0.05;**p<0.01

	MFTC		cMFTC		MT		cMT		cMF		ccMF	
	MC%	SRM	MC%	SRM	MC %	SRM	MC %	SRM	MC%	SRM	MC%	SRM
COR FLASH	-1.9*	-0.28	-2.7**	-0.34	-0.9	-0.19	-1.4	-0.22	-2.7*	-0.29	-4.0**	-0.33
SAG DESS	-2.9**	-0.35	-4.0**	-0.36	-2.0**	-0.38	-2.6**	-0.34	-3.7*	-0.30	-5.4**	-0.31
SAG DESS (odd)	-3.0**	-0.34	-3.8**	-0.35	-1.9**	-0.36	-2.5**	-0.34	-3.9**	-0.30	-5.3**	-0.30
SAG DESS (even)	-2.9**	-0.34	-4.2**	-0.36	-2.1**	-0.38	-2.7**	-0.32	-3.7*	-0.29	-5.8**	-0.32
COR DESS MPR	-2.5**	-0.32	-3.4**	-0.37	-1.6**	-0.34	-2.0*	-0.30	-3.5*	-0.29	-5.0**	-0.35

CONCLUSION: Higher rates of cartilage loss were observed with the DESS than with the FLASH, but the sensitivity to change was similar between the protocols. The baseline values of the FLASH and DESS were strongly, and the changes over 1 year were moderately correlated, suggesting that OAI results from analyses using these different acquisition protocols may be pooled. Using only every 2nd slice of the SAG DESS for computing ThCtAB did not negatively impact the sensitivity to change.

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PREDICTORS OF CARTILAGE THINNING AND THICKENING IN OA PARTICIPANTS

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INTRODUCTION: In a natural history trial it had recently been reported that few participants (25% of n=75) with symptomatic and medial radiographic knee OA showed significant cartilage thinning over 2 years in at least one medial femorotibial subregion using MRI, compared with the change in a healthy reference cohort (n=77). 15% of the OA participants displayed significant cartilage thickening in at least one subregion, and 60% no significant change in cartilage thickness. When evaluating whether DMOADs can prevent cartilage thinning (loss) or thickening (swelling or hypertrophy), it is important to predict which participants will change in which direction in the trial.

OBJECTIVE: To identify specific predictors of cartilage thickening and thinning in participants with OA.

METHODS: 152 female participants were followed over 2 years at 7 clinical centers using 3T MR imaging (1.0 mm coronal FLASHwe). 77 participants had no symptoms and no evidence of radiographic OA in either AP or Lyon Schuss radiographs, whereas 75 displayed symptoms and medial femorotibial radiographic OA. Subregional cartilage thickness (ThC) was determined in 5 tibial (MT) and 3 femoral (cMF) subregions from baseline and 2 year follow up images using custom software (Chondrometrics). OA participants with significant cartilage thinning, thickening or no change in any of the 8 subregions were identified based on comparison to the z-distribution of change in the healthy reference subjects. Receiver Operator Characteristic (ROC) analysis and Wilcoxon signed rank tests were applied to determine whether baseline measures of clinical and radiographic status, cartilage and meniscus morphology, cartilage composition and serum biomarkers discriminated between the groups mentioned above.

RESULTS: Areas under the curve (AUC) for predicting cartilage thinning or thickening and p-values (*<0.05;** <0.01;*** <0.001) for various comparisons are shown in Table 1. No significant differences between groups were found for the following biochemical biomarkers obtained from urine (u), plasma (p), or serum (s): uOsteopontin normalized to creatinine, uTIiNE.Cr, uTIIINE.Cr, pPGE2, p15HETE, sPIIANP, sIntactPINP, sCOMP, uAgg.Cr.

Table 1: AUC and p-values

Baseline characteristics	Healthy reference vs. OA no change	OA thinning vs. OA no change	OA thickening vs. OA no change	OA thickening vs. OA thinning
Age	0.61*	0.50	0.49	0.55
WOMAC function	0.87***	0.68*	0.69*	0.53
JSW (RX Lyon Schuss)	0.51**	0.74**	0.51	0.76*
Knee alignment (AAA)	0.62*	0.77**	0.55	0.68
ThC MT (MRI)	0.63*	0.57	0.55	0.56
ThC cMF (MRI)	0.63*	0.81***	0.59	0.76*
Meniscus morphology §	up to 0.65; *to**	up to 0.63	up to 0.59	up to 0.60
Mean dGEMRIC MFTC	0.73***	0.66*	0.61	0.60
Mean T2 MFTC	0.59	0.48	0.60	0.69
SD of T2 MFTC	0.57	0.66*	0.78**	0.65
Biochemical markers #	up to 0.72; *to***	0.64	0.68	0.73
sCTXI	0.49	0.65*	0.50	0.68

§: sublux. **, height *, %coverage **; # uTIINE.Cr***, pNPII*, pYNO2**, sCPII*, sPIIINP**, uCTXII.Cr***

CONCLUSION: Only few parameters (WOMAC function, JSW, knee alignment, ThC, T1 measured by dGEMRIC, T2 [SD only], and sCTXI) predicted significant cartilage thinning versus no change. ThC of cMF was the strongest predictor of cartilage thinning. Participants with significant cartilage thickening were identified by WOMAC function and the SD of T2 (versus those with no change) and by JSW and ThC of cMF (versus those with thinning).

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THE BM LESION OF OA: IS LESS FAT MORE RELEVANT THAN MORE WATER?

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INTRODUCTION: MRI of painful OA joints often reveals an increased aqueous signal in the subchondrium. Because the volume of this space is fixed, the increase in water implies that there is less fat. The pathogenesis of this change remains unclear but a consideration of subchondral structure and mechanics may provide useful insights to explain at least one cause of such lesions.

OBSERVATIONS:

1) The subchondrium is highly compartmentalized, fat-filled, and pressurized at rest through a surprisingly rich microvascular bed.
2) Impact loading distorts this region (without loss of volume) and further pressurizes its fatty contents.
3) Because fat is incompressible, much of the loading energy is transferred and distributed throughout the trabecular walls (from which it may then be recovered to provide “spring” to one’s step).
4) OA is sometimes complicated by painful intraosseous hypertension. This factor will then amplify the normal, barostatic response to load.
5) Resultant pressures appear to drive intravasation of marrow fat which then clears ultimately to the lung through venous drainage.
6) The displaced fat will be replaced by water, blood, and/or cells to create the BM lesion.

CONCLUSION: If an aqueous signal implies loss of critical, cushioning fat, the overlying cartilage may experience adverse physical and metabolic effects under load. Restoration of marrow fat may be at least as crucial (and perhaps as difficult) as restoration of cartilage in the ultimate repair of OA lesions.

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WHICH SUBCHONDRAL BONE MEASURE IS THE BEST PREDICTOR OF CARTILAGE DAMAGE?

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INTRODUCTION: It is widely accepted that subchondral bone plays a central role in the pathogenesis of OA. Evidence suggests that subchondral bone changes precede cartilage damage, indicating bone changes may be an early stage of OA. There are many features of subchondral bone involved in cartilage damage, such as bone area, BM lesions, and bone mineral density. It is unknown which of these subchondral bone measures is the best predictor of cartilage damage.

OBJECTIVE: To describe the association of baseline: 1) tibial bone area, 2) BM lesions, and 3) subchondral bone mineral density (sBMD), with knee cartilage defect progression and cartilage volume loss.

METHODS: A total of 338 adult males and females (mean age 63 years, range 52-79) were measured at baseline and approximately 2.7 years later. Tibial and femoral knee cartilage volume, tibial and femoral cartilage defects (range, 0-4), and tibial bone size were determined with MRI using a T1-weighted fat saturation 3-dimensional (3-D) spoiled gradient recall acquisition. Tibial and femoral BM lesions (range, 0-3) were determined with MRI using a T2-weighted fat saturation 3-D fast spin-echo sequence. Tibial sBMD of the right knee was assessed by dual energy x-ray absorptiometry (DXA).

Logistic regression analysis was used to examine the associations between increases in cartilage defects (increase versus no increase) and baseline bone measures. Multilevel mixed-effects linear regression was used to examine the association between change in cartilage volume and baseline bone measures.

RESULTS: For the medial compartment, 1) baseline tibial bone size was positively associated with increases in tibial cartilage defects [odds ratio (OR) 3.4 per change in SD, $P = 0.017$] and negatively associated with tibial cartilage volume change [standardized beta coefficient (β) = - 0.01, $P < 0.01$], independent to age, sex, BMI, baseline tibial cartilage defects, and other baseline bone measures.

2) Baseline tibial and femoral BM lesions were positively associated with compartment-specific cartilage defect increases (OR 1.8 per grade, $P < 0.01$; OR 2.4 per grade, $P < 0.01$, respectively) and negatively associated with compartment-specific cartilage volume change ($\beta = -0.007$, $P = 0.017$; $\beta = -0.004$, $P < 0.01$, respectively), independent to age, sex, BMI, baseline compartment-specific cartilage defects, and other baseline bone measures. Similar results were observed for the lateral compartment, except that baseline tibial bone size was not associated with tibial cartilage volume loss ($P = 0.763$).

3) sBMD at baseline was associated with increases in cartilage defects at the medial tibial site only (OR 1.5 per change in SD, $P < 0.01$). Baseline tibial sBMD was not associated with tibial cartilage volume loss.

CONCLUSION: BM lesions and tibial bone size independently predict cartilage damage and loss, suggesting both are important in the pathogenesis of osteoarthritis. sBMD predicts worsening of medial tibial cartilage defects; however, does not predict cartilage volume loss. Further research should examine different measurement techniques in assessing sBMD, possibly different regions of interest within the subchondral bone, to broaden the understanding of subchondral bone's role in osteoarthritis.

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THE RELATIONSHIP BETWEEN PREVALENT MEDIAL MENISCAL MUCOID DEGENERATION AND TEARS WITH CARTILAGE LOSS IN THE MEDIAL TIBIOFEMORAL COMPARTMENT: A TWO YEAR FOLLOW-UP STUDY USING 3.0T MRI

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INTRODUCTION: The role of the menisci in knee biomechanics include important functions such as load bearing, shock absorption, lubrication, and joint stability. Meniscal pathology is commonly observed in patients with and without radiographic knee osteoarthritis (OA). Mechanical impairment of the meniscus will alter the weight-bearing capacities of the knee joint, leading to damage in the articular chondral surface of the same compartment as well as in the subchondral bone, ultimately contributing to progression of OA.

OBJECTIVE: To investigate the association of different types of medial meniscal pathology with regional cartilage loss in the medial tibiofemoral compartment in subjects with and without knee osteoarthritis.

METHODS: A total of 152 women participated in a longitudinal 24-month observational study. Spoiled gradient recalled acquisitions at steady state (SPGR) and T2-weighted fat-suppressed MRI sequences were acquired. Four grades of meniscal lesions were assigned for the anterior horn, body, and posterior horn at baseline: 0 (normal), 1 (intrameniscal signal changes), 2 (single tears), and 3 (complex tears/maceration). Cartilage morphometry was performed at baseline and 24-month follow-up in different tibiofemoral subregions using segmentation and computation software. Multiple linear regression models (grade 0 medial meniscus as the reference group) were applied for the analysis with cartilage loss as the outcome. The results were adjusted for age, BMI, and medial meniscal extrusion.

RESULTS Cartilage loss at follow-up in the total medial tibia (0.04, p=0.035) and the external medial tibia (0.068, p=0.037) was significantly increased for compartments with grade 3 lesions only, compared with compartments with non-pathologic menisci. Cartilage loss at the external medial tibia appears related to tears of the posterior horn (0.074; p=0.025).

CONCLUSION: The protective function of the meniscus appears to be preserved even in the presence of intrameniscal signal changes and/or tears. Prevalent complex tears and meniscal maceration are associated with increased cartilage loss in the same compartment, especially at the posterior horn.

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MULTIVARIATE QUANTITATIVE MAGNETIC RESONANCE IMAGING PREDICTS WOMAC LEVELS: DATA FROM THE OSTEOARTHRITIS GLOBAL INITIATIVE

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INTRODUCTION: The OAI is conducting a large characterization effort in which the main product is a comprehensive set of databases that includes patient history, physical evaluation, joint health, nutrition, possible risk factors, putative biomarkers, and images. Nevertheless, imaging is very promising due its ability to fully characterize the stage of the disease using observable and reproducible radiological scoring. Furthermore, OA quantitative imaging analysis has advanced in recent years and plenty of new measurements have been proposed to yield light in understanding the disease progression. However, the importance and relevance of quantitative imaging has been questioned by the lack of clear association to how the patient feels and functions. This association deficiency may be due to the use of univariate analysis of imaging findings. Therefore, more powerful tools are needed to analyze to establish the relationship between multivariate measurements to symptomatic, diagnostic, or prognostic indicators.

OBJECTIVE: We propose to use a well know bioinformatics method to model an indicator of clinical value of imaging findings as a multivariate classifier coupled with an automatic variable selection approach. The multivariate variable selection technique used is capable of searching thousands of variable combinations to determine which subsets of variables are the most important for diagnosis/prognosis discrimination. We tested our approach to systematically find predictive quantitative imaging models of the symptomatic OA using total WOMAC levels.

METHODS: OA subject data and databases were downloaded from OAI website (Error! Hyperlink reference not valid.). Base line datasets JointSX00 and Image Set Release 0.D.1 were used for this study. From the JointSX00 dataset, the total WOMAC was selected as indicator of the degree of OA symptoms. The image analysis was done fully automated using iPAS-qAtlas software (IMITEK, Monterrey, Mexico). The software provided inter-bone distance measurements, cartilage morphological measurements, bone shape measurements as well as MRI signal properties at the tibia-femoral joint space. To associate variables that may predict WOMAC, we used our previously published software (GALGO) with a k-nearest-neighbor (KNN) classifier. To derive classes from WOMAC values, we hypothesized that the OAI measurements from individuals with lower WOMAC values should be clearly different than those with higher WOMAC values. Thus, we used the lower 10% WOMAC values and their respective samples as class 1 and higher 10% as class 2. Then, we challenged this assumption by taking lower 20% versus higher 20%, then 30% and finally 40%. Accuracy was estimated by the proportion of correctly classified subjects. Around 100 models were obtained for every class comparison to design a final summary model.

RESULTS: We obtained 81%, 75%, 73%, and 70% accuracy in the 10%, 20%, 30% and 40% partitions respectively. Therefore patients with lower and higher WOMAC values are easily distinguished by the information acquired in the image analysis. As an example, the three most important measures automatically selected for the 10% partition were trochlea curvature at layer, medial femur volume and lateral tibia cartilage volume.

CONCLUSIONS: The use of advanced multivariate bioinformatics methods in the OAI imaging release has provided an interesting insight regarding the imaging variables predicting joint symptoms as measured by the WOMAC scores. The extracted highly predictive models of the joint symptoms from the quantitative imaging included variables that confirm current understanding of the disease; but also highlighted variables that merit further evaluation as possible OA risk factors. On the other hand, the poor predictive value of cartilage thickness of symptomatic OA may indicate that more work is required to fully understand the association of cartilage loss to pain. Overall, this study suggests that the proposed methodology is viable and powerful enough to yield light in the epidemiology of OA with great potential for the design novel diagnostic and therapeutic procedures. Future work will be done to include the two year data and a larger imaging data set with the hope to find useful models aimed to the accurate characterization of symptomatic OA by imaging findings.

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SAME DAY T1ρ, T2 AND dGEMRIC MEASURES OF CARTILAGE POST-ACL INJURY

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INTRODUCTION: Early onset of OA can be detected from degeneration of cartilage, which involves loss of macromolecules from the extracellular matrix. Advances in MRI technology enable us to observe changes in glycosaminoglycan and collagen distribution *in vivo*, thus providing localized information on the state of cartilage health. T1□ MRI show promise as a noninvasive proteoglycan (PG) sensitive imaging method, as the exchange of protons between free water and macromolecules strongly influences this relaxation parameter. T2 imaging indicates hydration and the condition of the collagen matrix. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) reflects distribution of contrast agent in the joint inversely related to the presence of negatively-charged glycosaminoglycans.

OBJECTIVE: We hypothesized that each MRI protocol would 1) detect local cartilage injury, 2) measure changes over time, and 3) contribute a unique piece to the cartilage condition picture.

METHODS: Nine patients with acute ACL injury were imaged prior to ACL reconstruction surgery using 3 different MRI protocols to acquire quantitative relaxation parameters. These MRI were a fast-spin-echo-based T1□ sequence, a multi-echo multi-slice spin-echo sequence, and a T1-weighted inversion recovery sequence 90-120 minutes after intravenous injection of gadolinium contrast agent (Magnevist®) to obtain T1□, T2, dGEMRIC maps within a four-hour time frame. Scans were obtained using a Siemens 3T TIM Trio MRI scanner. For each patient, T1□ images with seven different spin-lock times (0, 5, 10, 20, 40, 60, and 80ms) and spin-echo images at seven different TE times (13.8, 27.6, 41.4, 55.2, 69.0, 82.8 and 96.6ms) were obtained at 3 slice locations. Two hours after Magnevist injection, dGEMRIC $T1_{GD}$-weighted images were obtained at 7 slice locations and six inversion times (30, 100, 250, 500, 1000, 1500ms) , each 0.3×0.3×3.0mm thick, from the trochlea to the edge of the lateral condyle, encompassing slice locations of the T1□ and T2 images. ACL reconstruction follow-up images were obtained at 3, 6 and 12 months using the same MRI protocols. Relaxation maps were generated by a curve-fitting program written in MATLAB. The average age of five male and four female patients was 24 years. Pixel-to-pixel comparisons between the protocol maps were linearly regressed to measure correlations.

RESULTS: Twenty same-day imaging sets were collected. Pixel-to-pixel comparison along co-registered profiles starting at the mid-anterior femoral condyle through the contused sulcus onto the weight-bearing region to mid-posterior condyle present relaxation times from the three MRI protocols collected in vivo on the same days. The methods detect local cartilage conditions to varying degrees. Bone bruising was not necessarily accompanied by immediately apparent changes to the overlying cartilage. Temporal changes were observed in the area of sulcus impact and in other cartilage regions during the follow-up imaging sessions. The expected negative correlations between the PG-sensitive T1□ and dGEMRIC images were not realized. Similarly, pixel-to-pixel correlations between T2 times and the other two sequences changed from patient to patient and time to time.

CONCLUSION: T2, T1□ and dGEMRIC imaging can capture changes occurring in ACL-injured knee joint cartilage, as evidenced by differences within and between patients and across time after the injury. However, differences in injury and healing/degeneration were uniquely presented by each method. These differences in capability may be beneficial in the design of patient-specific treatment protocols, at an early stage of the disease. Inconsistent correlations between the three MRI-weightings suggest each has distinctive components that influence their respective relaxation mechanisms. Changes in metabolic aging of cartilage such as total collagen and collagen cross-linking may provide PG-content ‘weighting’ that better correlates to MRI measurements. Presence of these entities can be measured in conjunction with current PG assays, and they may be correlated collectively by similar measures in the blood serum and synovial fluid.

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EFFECTS OF WEIGHT LOSS ON ARTICULAR CARTILAGE PROTEOGYLCAN CONTENT UTILIZING dGEMRIC AT 3T

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INTRODUCTION: dGEMRIC of the knee is used to assess the relative distribution of glycosaminoglycan in cartilage.

OBJECTIVE: To assess the effects of weight loss on dGEMRIC indices in obese subjects.

METHODS: Fifty-five subjects were recruited from laparoscopic adjustable gastric banding or exercise and diet weight loss programs. All subjects underwent MRI with standard dGEMRIC protocol at 3T (Magnetom Trio; Siemens, Erlangen, Germany) at baseline and follow up at 12 months. Double dose (0.2 mM/kg) $GdDTPA^{2-}$ was administered 90 minutes prior to imaging. Patients were required to walk for 15 minutes after injection. 2D single-slice dGEMRIC images were obtained in the medial and lateral sagittal planes, with FSE inversion recovery sequence with 5 inversion delays ranging from 50 to 2080msec (TR 2200 msec; TE 14 msec). Slices were 3 mm thick with in-plane resolution 275µm. The dGEMRIC indices were calculated after manual segmentation to obtain the medial and lateral dGEMRIC index (from the weight-bearing femoral cartilage and all the tibial cartilage). T1Gd maps were generated with pixel-by-pixel 3-parameter T1 fit using Matlab software (The MathWorks, Natick, MA). Regression analyses were used to assess the relationship between change in weight/ BMI and change in medial and lateral dGEMRIC index. Multivariate analysis adjusted for age, gender, BMI, and presence of clinical knee OA (ACR clinical criteria).

RESULTS: There were 37 females (67%); mean age was 50.9 ± 12.4 years and mean BMI at follow up was 39.5 ± 5.3. The mean medial and lateral sagittal dGEMRIC indices at baseline were 545 ± 84 msec and 539 ± 91 msec respectively. Fourteen patients (26%) met ACR clinical criteria for clinical knee OA and 24 (44%) patients underwent laparoscopic gastric banding surgery for weight loss. The mean absolute and percentage decrease in BMI was 3.7 (± 4.1) and 9.1 (± 10.0) respectively. Mean increase in medial and lateral dGEMRIC index at 12 months was 12.6 ± 106.0 and 22.8 ± 107.3 msec, respectively. Improved medial dGEMRIC index correlated positively with weight loss (r=0.32; p=0.021), weight loss percentage (r=0.35; p=0.011) and BMI loss (r=0.31; p=0.023) in univariate analysis. The degree of improvement in mean medial dGEMRIC index improved incrementally with increasing categories (quartiles) of weight loss; the highest quartile of weight loss had a mean improvement of 70.7 ± 106.0. In multivariate analysis, improved medial dGEMRIC index correlated positively with weight loss (r^2=0.26; p=0.009). The multivariate model that included age, gender, BMI, knee OA, knee range of motion, quadriceps strength and weight loss accounted for 27% of the variance in medial dGEMRIC (r^2=0.27; p=0.017). Similar results were identified for weight loss percentage and BMI loss in multivariate analysis. Change in lateral dGEMRIC index was not associated with weight loss, weight loss percentage or BMI loss in univariate or multivariate analysis.

CONCLUSION: This study is one of only a few reports of longitudinal assessment of dGEMRIC for assessment of proteoglycan content in knee articular cartilage. It is the first study to evaluate the impact of weight loss, and has shown promising results with improvement in medial sagittal dGEMRIC index in association with weight loss.

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PAIN, FUNCTIONAL LOSS AND RADIOGRAPHIC FEATURES IN KNEE OSTEOARTHRITIS - ANY LINKS?

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INTRODUCTION: Osteoarthritis (OA) is the most frequent form of arthritis and is a growing cause of social and economic burden to our aging society. Knee OA is particularly important in view of its high prevalence and association with severe pain and disability. In everyday clinical practice, however, there is an apparent discordance between radiographic and symptomatic knee OA.

OBJECTIVE: In this report, we describe a cross-sectional analysis designed specifically to assess the relationships between pain, function, and radiographic features of knee OA, which include the patellofemoral joint as well as the tibiofemoral joint, and individual radiographic features as well as a composite score.

METHODS: Both knees of 167 community-based patients with OA in at least one of their knees were assessed. Pain was measured by visual analog scale, and function was assessed using the functional domain of the Western Ontario and McMaster Universities Osteoarthritis Index. Anteroposterior standing radiographs with the knee in extension and lateral 30° flexion were obtained and assessed by two independent readers for the Kellgren & Lawrence score and for individual features (osteophytes, joint space narrowing, and subchondral bone sclerosis) in each compartment.

RESULTS: Knees with structural changes in both the tibiofemoral and the patellofemoral compartments were more likely to be painful and to be associated with loss of function than were knees in which only one compartment was affected. The individual feature most strongly associated with pain was subchondral bone sclerosis.

CONCLUSION: Studies exploring the associations between structural and symptomatic knee OA need to include an assessment of the patellofemoral compartment, and individual radiographic features rather than a global severity score should be considered in these studies.

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VOXEL-BASED ASSESSMENT OF DISEASE PROGRESSION IN ARTICULAR CARTILAGE WITH T2 FOLLOW-UP EXAMINATIONS: GETTING NEW DIAGNOSTIC INFORMATION FOR FREE

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INTRODUCTION: Although T2 has been demonstrated to be sensitive to the degradation of the collagen matrix of the articular cartilage [1−3], its use in clinical routine has not yet become established. However, T2 as a quantitative parameter has great potential for comparison of follow-up examinations, which has been poorly exploited due to the lack of adequate tools for comparison of T2 maps.

OBJECTIVES: To develop a method for voxel-based comaprisson of follow-up examinations and test it on matrix associuated autologous transplanted (MACT) patients.

METHODS: In follow up examinations two data sets of the same subject acquired at two different time points, which will be termed 1 for baseline and 2 for follow-up, must be compared. The first step is to register the images in order to compare the T2 values of the same voxel. A rigid 3D registration method with a registration error under 25% of the voxel size was used [4]. After registration, for each voxel there are two T2 values, $T2_1$ and $T2_2$, which may differ. To be sure that the two T2 values really represent a significant change in T2, the total errors of T2, for each $T2_1$ must be known.
To estimate the total errors of T2, the tibial cartilage of healthy volunteers (*n*=12) and early OA patients (*n*=12,KL=1-2) were repeatedly imaged with a multi-slice multi-echo SE sequence (TE/TR = 13.2/3500 ms, echo train length = 8, echo spacing 13.2 ms, FOV = 256×256, in plane resolution = 0.61×0.61 mm, slice thickness = 3 mm). Volunteers were imaged at three different time points whereas patients were imaged twice. All images of the same volunteer/patient were pairwise registered and used to calculate the measurement error for each $T2_1$, $\sigma(T2_1)$. Once $\sigma(T2_1)$ is known, for each measured $T2_1$ the range of the $T2_2$ expected in the same voxel in a follow-up examination is $T2_1 \pm 2\sigma(T2_1)$, assuming no change has occurred. If $T2_2$ is outside this range a change is likely ($P<0.05$) to have been occurred.
A 2σ-significance chart has been introduced to link the changes in T2 with the changes in cartilage. The 2σ-significance chart is constructed by combining $\sigma(T2_1)$ with the 99% percentile of healthy T2 values of the T2 values measured in all healthy volunteers (Fig. 1A). The 2σ-significance chart allows differentiating between 7 different diagnostic outcomes.

The utility of the 2σ-significance chart were tested on 5 MACT patients. Patients were examined 1.5 (baseline), 3, 6 and 12 months after intervention. The state of the knee was assessed at 6 and 12 months after intervention with the international knee documentation committee (IKDC) questionnaire. The mean significant T2 change, ΔT2, is defined as the mean difference in T2 of all the voxels which had significantly change its T2. Averaged ΔT2 over all follow-ups and bulk T2 was correlated with the IKDR score of the knee.

RESULTS: Measurement errors are represented in Fig. 1A. The measured 2σ-significance chart is represented in Fig. 1B. Fig. 1C shows the example of the results of the significance changes in T2 in follow-up examinations. The color encoding of the regions is consistently used in the colour maps for the patient in the example of Fig. 1C. In this case the differences in T2 demonstrated significant healing of the lesions located near to the bone-cartilage interface at 12 weeks, and growth of the lesion located at the cartilage surface. Healthy voxels surrounding the surface lesion at baseline turned to be pathological in the first follow-up. The significant T2 reduction in pathological voxels at the cartilage surface may be an early sign of the healing confirmed by the follow-up at the 24 week. The averaged ΔT2, demonstrated a significant ($P>0.01$) correlation with the results of the IKDC evaluation form (r2=0.72). Using the bulk T2 did not revealed any significant correlation.

CONCLUSIONS: The voxel-based method for evaluation of T2 follow-up examinations presented here greatly simplifies the evaluation of follow-up examinations providing new diagnostic information. Although the diagnostic relevance of the method must still be confirmed in OA patients, the first promising results in MACT patients open a new way to look at T2 (or any other MRI parameter) maps.

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REPRODUCIBILITY OF KNEE CARTILAGE T2 MEASURES ACROSS DIFFERENT VENDORS' 3.0T SCANNERS

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INTRODUCTION: T2 relaxation is the MRI marker of cartilage quality used in the OAI. The OAI is conduced on 4 Siemens 3T scanners, but Philips Medical Systems and GE Healthcare also manufacture 3T scanners. The ability to conduct multicentre and multivendor trials would have the potential for reducing study time and cost.

OBJECTIVES: 1) determine whether cartilage T2 values are comparable between the different vendors; and 2) determine whether the reproducibility of cartilage T2 values between scanners is comparable with reproducibility across multiple sessions on a single scanner.

METHODS: 12 subjects (9 male, 3 female) with symptoms of knee OA had their most symptomatic knee scanned on each of 3 vendors' 3.0T scanners. The three systems used are located in the UK: Manchester (Philips), York (GE), Liverpool (Siemens). The OAI study protocol was used for the Siemens platform. With collaboration from Philips and GE, OAI-equivalent protocols were optimised for the respective platforms. The T2 map sequence used was a multi-slice multi-echo (MSME) sequence. Subjects were non-weight-bearing for 30 minutes prior to each scan. Intra-scanner reproducibility data were obtained using 5 subjects on the Philips scanner only.
Manual cartilage segmentation of the first TE images was performed by a single observer blind to subject identity using proprietary software (Endpoint, Imorphics Ltd. Manchester, UK). To avoid partial volume effects, only voxels wholly contained within the segmentation were included in the analysis. Transverse relaxation rate (R2) values were obtained by fitting the log of the signal values to the corresponding TE values using linear least squares fit. Statistical analysis was performed using R2 values and the results inverted to provide T2 values for presentation.
RESULTS: Inter-Scanner Variability (n=12): Inter-scanner knee R2 RMS COVs for Philips vs. Siemens was similar to the Philips intra-scanner inter-session values. No significant difference was observed for MT and P regions (*p>0.05, see table). GE knee T2 values were systematically lower, producing mean differences with other scanners in the range 5.4–10.0ms

Region	Scanner Pair	R2 RMS COV	T2 Mean Difference (ms)	95% Confidence Limits (ms)		Paired t-test p-value
F	S vs. P	5.5%	2.8	-2.3	7.9	0.003
	S vs. G	16.0%	10.0	5.3	14.6	0.000
	P vs. G	12.2%	7.1	1.9	12.4	0.000
MT	S vs. P	4.2%	-1.2	-5.7	3.3	0.095*
	S vs. G	11.5%	5.4	0.2	10.7	0.000
	P vs. G	13.4%	6.6	1.1	12.2	0.000
LT	S vs. P	8.6%	-2.8	-11.2	5.6	0.045*
	S vs. G	12.6%	5.9	-0.4	12.2	0.000
	P vs. G	17.5%	8.7	2.0	15.3	0.000
P	S vs. P	4.8%	0.8	-5.0	6.7	0.355*
	S vs. G	18.1%	8.7	-1.6	19.0	0.000
	P vs. G	16.1%	7.8	0.0	15.7	0.000

Intra-Scanner Reproducibility (Philips n=5): Philips intra-scanner R2 RMS COVs were <3% (intra-session) and 3.2–6.3% (inter-session) for all regions.

CONCLUSION: This is the first study to investigate differences in cartilage T2 mapping between scanners of different vendors at 3T. In vivo cartilage T2 analysis poses many challenges which limit accuracy and reproducibility of measurements, e.g. stimulated echoes, magnetisation transfer, partial volume. Inter-scanner precision errors can be comparable to intra-scanner precision, however, significant inter-scanner differences can exist.
SPONSOR: AstraZeneca (Cheshire) provided financial support and Imorphics Ltd. (Manchester) provided image analysis services.ACKNOWLEDGMENTS: C. Bos (Philips Medical Systems), S. Dezonie (GE Healthcare), G. Green (YNIC, York). L. Gregory (TIU, Manchester).
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DETAILED DIGITAL ANALYSES OF HIP AND KNEE RADIOGRAPHS IN AN EARLY OSTEOARTHRITIS COHORT (CHECK) PROVIDE INDIVIDUAL JOINT CHARACTERISTICS INDEPENDENT OF DISEASE

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INTRODUCTION: Detailed digital image analysis techniques are developed for more precise evaluation of radiographic OA, resulting in continuous measures of separate features of OA.

OBJECTIVE: To evaluate whether accurately measured radiographic features by digital analyses 1) are related to the severity of OA and 2) represent joint characteristics of an individual.

METHODS: In the CHECK (Cohort Hip & Cohort Knee) study 1002 participants with early complaints related to OA were included for evaluation of clinical and radiographic features of OA during 10 years of follow-up. At baseline mean age of participants (79% female) was 56(±5) years and 45% of participants suffered from pain in hip(s) and knee(s), 36% in knee(s) only, and 18% in hip(s) only, with a median VAS intensity of 3 (2-5). Baseline standardised radiographs (AP pelvis and PA semiflexed) were analysed with digital image analysis using Holy's software-β19/20™ and Knee Images Digital Analysis (KIDA) providing continuous measures of minimum JSW and mean JSW of hip radiographs and minimum and mean JSW, total osteophyte area and mean bone density (BD) of knee radiographs. Both methods have shown to measure characteristics of OA in established disease. At baseline 93% of participants had no or doubtful OA in hips or knees (KLG 0&I) and only 7% had minimal or moderate OA (KLG II&III). Outcome measures of digital analyses were compared with conventional KLG to study validity of measuring individual joint characteristics. Importantly, it was evaluated whether these separate outcomes represented joint characteristics of the individual and/or were related to the disease. In this case, radiographic OA will affect normal anatomy of an individual resulting in a lower correlation between joints. Comparisons were made between contralateral joints (left vs. right hip and left vs. right knee), ipsilateral joints (e.g. left hip vs. left knee) and diagonal joints (e.g. left hip vs. right knee) for all participants and for subgroups of participants without (KLG 0&I) and with (KLG II&III) radiographic OA. Pearson correlation coefficients were determined for comparison of digital analyses with KLG and for comparison between joints within participants.

RESULTS: 1) In these participants with early complaints related to OA, significant correlations were found between the conventional KLG and the separate features as measured by digital image analyses: R=-0.36 for minimum JSW and R=-0.24 for mean JSW of the hip (both $p<0.001$). For the knee correlations found were R=-0.19, -0.19, 0.36 and 0.10 for minimum and mean JSW, osteophyte area and BD respectively, all $p<0.001$. Irrespectively, within one KLG a large variation was found for outcome measures of the digital analyses. 2) Overall significant correlations between individual radiographic features of different joints (contralateral, ipsilateral and diagonal) within participants were found. Strong correlations were found in the subgroup with KLG 0&I, especially between contralateral joints: correlations for minimum and mean JSW of the hips, and minimum JSW, mean JSW, osteophyte area and BD of the knees were R=0.72, 0.81, 0.70, 0.71, 0.56, and 0.89 (all $p<0.001$) respectively. Importantly, in the subgroup with radiographic OA (KLG II&III) most correlations disappeared, suggesting a disruption of the normal anatomy by asymmetrical appearance of radiographic features in isolated joints of individual participants.

CONCLUSION: In an early OA cohort accurately measured radiographic features reveal generalised radiographic joint characteristics for individuals independent of OA, and asymmetry in radiographic joint characteristics in case of manifestation of OA.

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A COMPARISON OF METHODS FOR MEASURING T2 DECAY TIMES

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INTRODUCTION: T2 decay times in articular cartilage have been correlated with variations in macromolecular concentration, collagen orientation and structure, and tissue hydration. The mathematics involved in calculating T2 are straightforward, but the choice of MR pulse sequence is not. Many different pulse sequences have been used in the literature ranging from dual-echo FSE sequences to several single-echo spin-echo sequences with varying echo times.

OBJECTIVE: The main objective of this study is to determine the accuracy of different MRI pulse sequences, and what effect different imaging parameters have on the calculated T2 decay times.

METHODS: Seventy vials with varying concentrations of $CuSO_4$ were placed in a container and imaged in a GE Twin Speed HDx 1.5T magnet. The container was oriented with the vials were standing vertically within the magnet. All images were in the coronal plane with a slice thickness of 3.5mm, matrix of 256x256 and FOV of 38cm (Figure 1). To obtain a "gold standard" for the T2 decay times, 8 spin-echo sequences were collected with TR/TE = 1500ms/10, 20, 30, 40, 50, 60, 80 and 100ms. Two four-echo spin-echo sequences were collected with TR/TE of 1500ms/16,32,48,64ms and 1500ms/20,40,60,80ms. In addition, three dual-echo FSE sequences were collected with TR/TE of 4500ms/16,99ms, 4500ms/24,59ms and 4500ms/16,82ms. For the four-echo sequences, T2 decay times were calculated using all four echoes and recalculated utilizing only the final three echoes. The spin-echo sequences were imaged with and without fat saturation (FS). All FSE sequences used an echo train length (ETL) of 8. For the FSE sequence with echoes of 18 and 82ms, an additional series was collected using an ETL of 4. Single-slice data and multiple-slice data were collected.

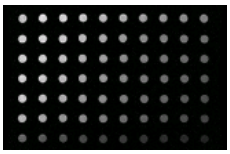

Figure 1 – One coronal slice of vials with TR/TE = 1500ms/80ms

RESULTS: The T2 decay times calculated for the vials using the "gold standard" technique ranged from 39ms to 685ms. The relatively long T1 values may corrupt the results for the longest T2 decay times. To account for this, the vials were separated into three groups: Group 1 (N=31) has all vials with T2 values below 100ms, Group 2 (N=25) has vials with T2 values between 100 and 200ms, and Group 3 (N=14) consists of all vials with T2 values above 200ms. A sampling of the results is presented in Table 1.

	4 echoes (16,32,48,64) FS	3 echoes (32,48,64) FS	3 echoes (32,48,64) No FS	3 echoes (32,48,64) No FS, 1 slice	FSE (18,82) FS, ETL=8	FSE (18,82) FS, ETL=4
Group 1	-17.29%	-6.71%	-11.37%	-28.51%	-2.56%	-0.28%
Group 2	-31.40%	-20.22%	-14.57%	-41.31%	-6.55%	-4.90%
Group 3	-52.48%	-40.97%	-3.48%	-61.32%	-12.58%	-13.51%

Table 1 – The results represent the percent difference between the "gold standard" calculated T2 value and the T2 value calculated from the specified series, averaged over all vials within the group.

CONCLUSION: The most accurate sequence that was tested for calculating T2 decay times less than 200ms was the dual-echo FSE sequence with echo times of 18 and 82ms and an ETL of 4. The most accurate sequence tested for calculating T2 decay times greater than 200ms was the 4-echo spin-echo sequence without fat saturation. The least accurate sequence for calculating T2 decay times was the 4-echo single-slice spin-echo sequence. When imaging the knee, there are many factors to account for including chemical shift artefacts, blurring from large echo train lengths, and imaging time. The next step is to repeat the experimenty on a smaller phantom in a knee coil, and then on human knees.

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EFFECT OF KNEE ALIGNMENT ON T2 RELAXATION TIME OF ARTICULAR CARTILAGE

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INTRODUCTION: Varus and valgus malalignment of the knee increases the risk of medial and lateral OA progression, respectively. The T2 relaxation time of MRI correlates with collagen content and hydration of cartilage, as well as with the integrity and arrangement of the collagen network. It may provide a sensitive tool to detect early degenerative changes in articular cartilage before they are seen on clinical MRI.

OBJECTIVE: To assess the influence of knee alignment on T2 relaxation time of femoral and tibial cartilage.

METHODS: Thirty patients (17 male, 13 female; mean age 49.9 yrs) with knee symptoms and 20 young asymptomatic volunteers (10 male, 10 female; mean age 22.5yrs) were enrolled in the study. For patients, knee alignment was measured from standing extended view digital radiographs. The anatomical axis was defined from the middle of the shaft of bone, 10 cm from the knee joint to the center of the tibial spines. The angle was used to divide the patients into varus (angle <2.2°) and valgus (angle ≥2.2°) groups (Hunter et al. 2007).

MRI was conducted using two GE Signa 1.5T scanners (GE Healthcare, Milwaukee, WI) equipped with a transmit/receive knee coil. T2 relaxation time was determined using a sagittal multi-slice multi-echo spin echo sequence (TR/TE=1000/10-80ms, ETL= 8, FOV=140mm, 256×256 matrix, 0.55-mm in-plane resolution, 3-mm slice thickness) with an improved slice profile. T2 relaxation times were determined from the weight-bearing femoral and tibial cartilage at the center of the condyles. Tibial cartilage was further divided into anterior, central and posterior regions of interest (ROIs). Superficial and deep parts of the cartilage were separately analyzed. The non-parametric Mann-Whitney -test was used to compare the T2 values of the varus and valgus groups with those of asymptomatic volunteers, with p-values less than 0.05 considered as an indication of statistical significance.

RESULTS: 19 patients had varus and 11 patients had valgus alignment. Varus alignment resulted in significantly longer T2 values in the deep part of medial femoral condyle when comparing to the control group (controls: 41.6±3.1ms, varus patients: 50.0±4.9ms). Varus alignment also contributed to higher T2 values in all ROIs of the medial tibial cartilage (controls: 44.1±1.7ms, varus patients: 52.1±2.2ms). Additionally, the varus group had longer T2 values at all deep ROIs of the lateral tibial compartment (controls: 40.4±1.6ms, varus patients: 46.6±2.7ms) and anterior superficial ROI of the tibia as compared to controls (controls: 43.8±3.3ms, varus patients: 49.0±7.8ms).

Valgus alignment showed a longer T2 laterally in deep part of the central tibial cartilage (controls: 38.5±3.3ms, valgus patients: 46.9±6.8ms), but no changes were seen in femoral cartilage. Longer T2 values were also observed medially in all ROIs of the tibial cartilage (controls: 44.1±1.7ms, varus patients: 51.3±3.5ms).

CONCLUSION: The alignment of the knee is known to affect the loss of cartilage in OA. A one year follow-up study reported greater mean cartilage loss in the medial than in the lateral compartment (Eckstein et al. 2008). In a two-year follow up study, varus alignment caused both femoral and tibial cartilage loss in medial compartment, while valgus alignment caused only tibial cartilage loss (Cicuttini et al. 2001). The present study suggests that alignment also affects the internal structure of cartilage, as measured by T2 relaxation time mapping. In varus alignment, T2 relaxation times were longer both in femoral and tibial cartilage of the medial compartment when compared to asymptomatic young volunteers. Valgus alignment showed longer T2 values only in tibial cartilage. Localized assessment of T2 relaxation time seems to provide a sensitive tool to detect early degenerative changes in OA.

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LONG-TERM AND SHORT-TERM REPRODUCIBILITY OF T2 RELAXATION TIME IN HMAN KNEE CARTILAGE

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INTRODUCTION: T2 relaxation time of articular cartilage has been reported to reflect the orientation and concentration of collagen fibrils. The reproducibility of T2 in human patellar cartilage has been reported to be close to 5%. However, the patellar cartilage is the thickest one in the knee, and the reproducibility in other articular surfaces has not been studied earlier.

OBJECTIVE: To investigate the long term and short reproducibility of the T2 measurements at different knee joint surfaces in asymptomatic volunteers.

METHODS: The right knees of nine asymptomatic volunteers (age 25-38 years, normal weight, 5 male, 4 female) were imaged at 1.5 T (GE Signa HDx, GE healthcare, Milwaukee, WI, USA) three times with time intervals of one week and two weeks. To observe short-term reproducibility, the measurements were repeated three times within one session for four volunteers. The positioning of the knee was controlled by using a leg holder and a custom-made inflatable cushion. All measurements were performed by the same person. T2 relaxation time was mapped using multi-slice multi-echo spin echo sequence (TR=1000 ms, TE=10-82 ms, ETL=8, 3-mm slice thickness FOV=12 cm, matrix size 256*256) in axial and sagittal directions. Single slices through the center of the lateral femoral condyle and from the center of the patella were analyzed. Cartilage was manually segmented into superficial and deep ROIs at different topographical locations.The absolute reproducibility, as measured by root-mean-square coefficient of variation (CV_{RMS}) was evaluated. To evaluate the difference between the long-term and short-term reproducibility, Wilcoxon signed rank test was used.

RESULTS: The results for superficial and deep regions are shown in Table 1. For bulk T2, the long-time reproducibility was 3.2%, 5.4% and 3.7%, and the short-term reproducibility was 3.9%, 3.9% and 3.4% for femoral, tibial and patellar cartilage, respectively. There were no significant differences between long-term and short-term reproducibility in superficial or deep cartilage when comparing CV_{RMS} values.

Table 1. Long-term and short-term reproducibilities for different regions of knee cartilage.

Region	Layer*	CV_{RMS} (%) long-term	CV_{RMS} (%) short-term
Lateral Femoral Condyle			
anterior aspect of trochlea	s	4.9	6.1
	d	7.3	5.4
posterior aspect of trochlea	s	9.9	11.6
	d	14.3	13.9
anterior central part	s	6.3	8.7
	d	12.7	13.9
posterior central part	s	4.4	4.1
	d	8.4	5.1
anterior posterior part	s	3.8	3.2
	d	3.8	4.2
posterior posterior part	s	5.1	2.5
	d	4.4	5.1
Lateral Tibial Condyle			
anterior part	s	13.2	12.7
	d	23.1	19.4
central part	s	7.6	8.4
	d	10.2	19.4
posterior part	s	4.3	5.9
	d	8.8	8.0
Patella			
lateral facet	s	3.3	6.4
	d	5.4	3.6
lateral apex	s	2.9	5.2
	d	5.3	4.9
medial apex	s	9.1	4.8
	d	6.4	7.4
medial facet	s	6.2	6.2
	d	7.1	8.1

* s - superficial 50% of tissue, d - deep 50% of tissue

CONCLUSION: The current results show mostly good reproducibility. However, there were remarkable variations between different topographic locations. The poorest reproducibility was found in anterior part of tibia, which is probably due to the small size and varying shape of the region. The best mean reproducibility was found at patella, where the cartilage is thick. Similar results have been reported earlier for dGEMRIC measurements of cartilage. T2 is probably more sensitive to patient positioning as compared to, eg., dGEMRIC because of the magic angle effect. The inter-examiner repeatability of segmentation in T2 measurements is reported to be 2-3%. The current results suggest that with careful patient positioning T2 at the different cartilage surfaces of the knee can be measured with good reproducibility.

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DEPTH-WISE TEMPORAL DYNAMICS OF Gd-DTPA^{2-} IN FEMORAL ARTICULAR CARTILAGE

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INTRODUCTION: dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) technique has been developed to assess GAG content of articular cartilage. Based on the previous studies, the ideal imaging time for knee joint after contrast agent injection has been assessed to be two hours, and full thickness regions of interest have been analyzed.

OBJECTIVE: To investigate the temporal dynamics of the contrast agent over time at different depths in cartilage.

METHODS: Fifteen healthy (symptomless) volunteers were imaged using single-slice inversion recovery spin echo sequence (TR = 2000 ms, TE = 15 ms, TI = 100, 200, 400, 800 and 1600 ms, matrix = 256x256, FOV = 12x12 cm, in-plane resolution 0.47 mm, slice thickness = 3 mm). A sagittal slice was localized to cover the middle part of lateral femoral condyle. Three regions of interest covering a layer of the most deep, middle and superficial cartilage were segmented manually on the weight-bearing femoral condyle. Triple dose (0.3 mM/kg) of Gd-DTPA^{2-} (Magnevist, Schering, Germany) was used, and the measurement was repeated after 1, 2, 3 and 4 hours after contrast agent injection, and the approximated Gd-DTPA^{2-} concentrations were calculated. To test the significance of the differences between the time points and at different cartilage depths, the Wilcoxon signed rank test and Mann-Whitney test were used, respectively.

RESULTS: A significant difference ($p<0.01$) was observed between pre-contrast T1 at different cartilage depths. Gd-DTPA^{2-} concentration increased until two hours in the superficial cartilage, and until three hours in the middle cartilage (Figure 1). For deep cartilage, the Gd-DTPA^{2-} concentration continued to increase until four hours. Until three hours, there is significant difference in the Gd-DTPA^{2-} concentration between the depth-wise regions. Between three and four hours, the Gd-DTPA^{2-} concentration begins to decrease in the superficial cartilage, while there still is a significant increase in the deep cartilage.

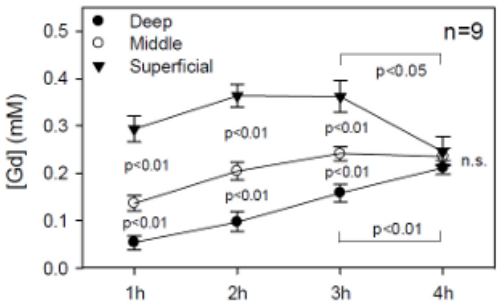

Figure 1. Gd-DTPA^{2-} concentration in femoral cartilage at different depths as a function of time after contrast agent injection.

CONCLUSION: Current results suggest that most of the contrast agent enters the cartilage from the synovial side, whereas the uptake from the bone is negligible. Based on the current results, the ideal time point to observe cartilage seems to be differ as a function of cartilage depth and thickness. Furthermore, the observed difference between superficial and deep pre-contrast T1 values suggests that the analysis of bulk cartilage regions of interest may not be the optimal way of estimating the GAG content, and that the post-contrast T1 alone doesn't provide all needed information for cartilage evaluation. The present results suggest that applying the dGEMRIC method for separate cartilage layers at different depths could provide additional information about the status of the cartilage.

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DELAYED GADOLINIUM ENHANCED MRI OF MENISCUS: DIFFERENCES IN OA

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INTRODUCTION: Osteoarthritis (OA) is considered a multisystemic disease and its origin and progression are believed to be attributable to disease in one or more tissues in the joint such as articular cartilage, sub-chondral bone, synovium, capsule and meniscus (Radiology 2008. 249:591-600). Meniscus is a crucial load-attenuating fibrocartilage in the knee.

Delayed gadolinium enhanced MRI of cartilage (dGEMRIC) has been widely applied in articular cartilage, and demonstrated as an effective method for determination of glyconsaminoglycan (GAG) levels within the joint cartilage. Even though it is known that meniscus contains much less GAG (Biochem J 1980; 185:705), it has been shown that T_1^{Gd} (dGEMRIC index) in the meniscus demonstrates a weak but statistically significant correlation with T_1^{Gd} in articular cartilage (Arthritis Rheum. 2007;56:1507). This observation, we hypothesize, is related to the fact that contrast uptake in dGEMRIC is determined by both transport of Gd in to and charge distribution within the tissue, both of which can potentially change with OA.

OBJECTIVE: To perform retrospective analysis of T_1^{Gd} in menisci (from subjects previously studied for dGEMRIC of the articular cartilage of the knee (Proc. ISMRM. 15 (2007) p. 3812)). We have specifically compared contrast uptake with an ionic and a non-ionic contrast agent.

METHODS: **Subjects:** Data from eighteen subjects, including 10 patients with self reported OA and 8 healthy subjects without evidence of OA (HS) were included. **Imaging:** All subjects had post contrast studies at 120 min, using 0.2 mmol/kg $Gd(DTPA)^{2-}$ (Magnevist) as ionic and Gd(DTPA-BMA) (Omniscan) as non-ionic contrast agent respectively. The acquisition related specific information can be found in previous report (Proc. ISMRM. 15 (2007) p. 3812). **Data analysis:** ROIs for T_1 mapping were defined in the meniscus (anterior and posterior horns of both medial and lateral condyles) and weight-bearing regions of the articular cartilage (the femur and tibia of both medial and lateral condyles). Each meniscus horn was further subdivided as the outer region (~ peripheral ¼ of the horn) and the inner region (rest of the meniscus) separately. T_1 mapping was performed with a custom software analysis routine written in MATLAB (The Mathworks; Natick, MA).

RESULTS: Consistent with the previous report, we found a relatively weak but statistically significant correlation between T_1^{Gd} in meniscus and articular cartilage with both $Gd\text{-}DTPA^{2-}$(Figure 1) and Gd(DTPA-BMA). We also found a high degree of correlation between T_1^{Gd} with ionic and non-ionic agents (Figure 2.a) implying minimal charge dependence (Figure 2.b).

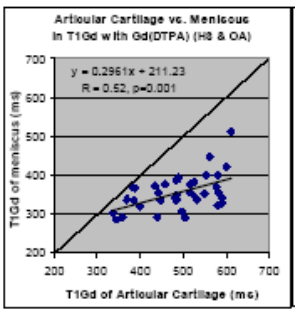

Figure 1

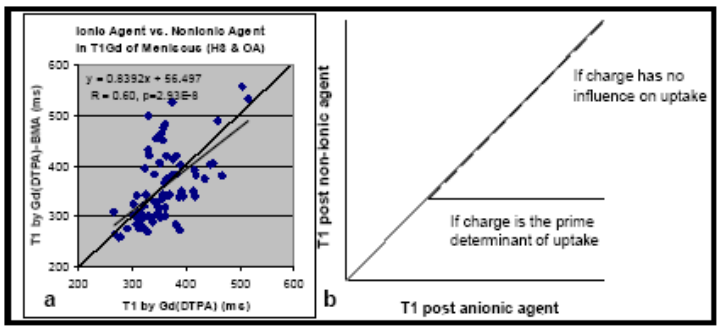

Figure 2

CONCLUSION: The uptake of Gd in the meniscus is dominated by transport over the charge based distribution related to GAG. This is supported by several observations including: Figure 2; a similar relationship as in Figure 1 with Gd-DTPA-BMA; no difference between the two zones within the meniscus - inner zone known to contain more GAG (J Orthop Res 1997; 15:213; 3); difference in uptake between OA and HS was higher with Gd(DTPA-BMA) (16 *vs.* 7%) compared to $Gd\text{-}DTPA^{2-}$. This suggests the correlation in Figure 1 to be related to primarily transport of Gd in to the cartilage.

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FAST 3D T_1 MAPPING FOR DGEMRIC BY VARIABLE FLIP ANGLE APPROACH: NEED FOR B_1 CORRECTION

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INTRODUCTION: Delayed gadolinium enhanced MRI of cartilage (dGEMRIC) is a technique for detecting the loss of glycosaminoglycans (GAGs). This technique requires quantitative T_1 mapping to determine GAG level within joint cartilage. Most of the reported work on dGEMRIC has been using standard two-dimensional inversion recovery turbo spin-echo (2D IR-TSE) or three-dimensional (3D) sequences (such as inversion recovery spoiled gradient echo [JMRI 2006 24: 928] or look locker (3D LL) [Invest Radio. 2006; 41:198; 4] to acquire quantitative T_1 mapping. The typical acquisition times for these different approaches are: 10 min for 1 slice with 2D IR-TSE, 20 min for 3D IR-SPGR and 10 min for 3D LL. 3D Variable flip angle approach with just 2 flip angles is an attractive technique with acquisition times of less than 5 mins for similar spatial resolution and requires *no* custom sequences. However, previous experience with this method demonstrated adequate accuracy of T_1 measurements in phantoms but not *in vivo* [Proc. ISMRM 2008, page 328]. We hypothesized that one of the probable causes for this is B_1 inhomogeneity which can vary the flip angle locally. B_1 variations exist due to slice profile effects depending on the specific shaped pulses used and the inherent B_1 inhomogeneities depending on the coil and electrical properties of the object.

OBJECTIVE: To investigate the slice to slice variation in T_1 measured by VFA approach using selective pulses (Sel), non-selective (NS) pulses and with B_1 correction (Cor).

METHODS: The study was performed on a 32-channel 1.5 T MR system (Magnetom Avanto, Siemens, Erlangen, Germany) using a commercial transmit/receive (T/R) extremity knee coil. 2D IR-TSE and 3D VFA sequences were applied to a gel phantom. A vendor implemented two FA acquisition with inline T_1 mapping was used. The protocol includes an inline calculation of optimal flip angle combination based on an estimated T_1 (ET_1) value which was set to 500 ms. The parameters for the sequence: TR/TE = 15/3 ms, matrix size = 384x384, slice thickness = 3mm, bandwidth = 210 Hz/pixel. B_1 inhomogeneity was estimated using a stimulated echo approach adding 39 s to the acquisition time of 4 min 7 s. The slice position of 2D IR-TSE was matched with the corresponding image within the 3D volume acquired using VFA method. The parameters of 2D IR-TSE were TR/TE=2200/13ms, TI=1680, 650, 350, 150, 50 ms, matrix size=384x384, slice thickness=3mm, FOV = 16cm.A phantom consisting of 9 tubes with 2% agar gel doped with varying concentrations of $GdDTPA^{2-}$ (Magnevist, Berlex, NJ) was was used to compare measurements with the 3D VFA approach against 2D IR-TSE technique and to study slice to slice variations due to B_1 variations.

RESULTS: Figure 1 illustrates the improvement in the slice to slice variation in T_1 values with B_1 correction. Figure 2 illustrates the agreement in T_1 measurements between the 3D VFA and 2D IR techniques. It is clear B_1 correction makes the T_1 values more accurate for both Sel and NS pulses.

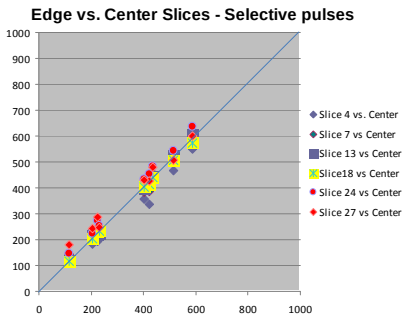

Figure 1

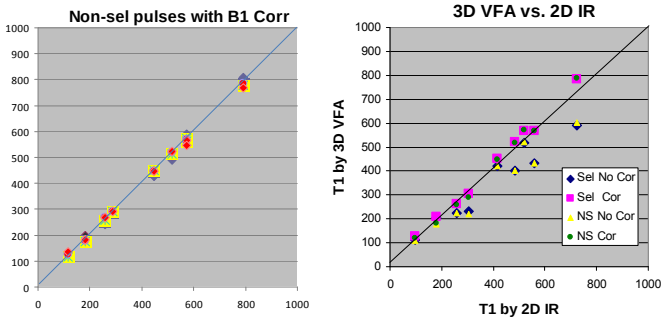

Figure 2

CONCLUSION: Combining non-selective pulses and vendor implemented B_1 correction improves the accuracy of T_1 measurements through out the 3D volume.

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TITLE: LOSS OF KNEE CARTILAGE IS LINEAR IN WOMEN WITH OSTEOARTHRITIS OVER 2 YEARS

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INTRODUCTION: Poor understanding of the natural history of spatial loss of articular cartilage in knee OA makes it difficult to relate diagnosis to prognosis, and difficult to personalize treatment in OA. Statistical Shape Modelling of MRI data can describe the pattern of change as the disease progresses.
OBJECTIVE: To evaluate the redistribution of articular cartilage thickness at baseline, 12, 18 and 24 months in females with knee osteoarthritis.

METHODS: A convenience group of 29 females was identified from the OAI progression group 0.B.1 and 1.B.1. The subjects chosen had MRI scans at baseline, and at 12, 18 and 24 months. They were selected because they had medial osteophytes at baseline, and medial JSN of OARSI grade 1 -3. BMI average was 31.2 (range 25-45). Images were manually segmented using EndPoint software (Imorphics, Manchester, UK), by trained segmenters blinded as to time point, but not to subject. A dense set of anatomically corresponded points was automatically identified on the femur and tibia bone surface of each image, allowing mapping of cartilage change both within and across subjects. Average thickness (ThCtAB) of the cartilage for each major compartment of the femur and tibia was calculated, and loss between the baseline and follow-up assessed using paired t-tests, with results expressed as a percentage of the baseline mean. At each point at which the thickness of cartilage was measured, the standardized response mean at each point across the population were calculated.

RESULTS:

		12 months		18 months		24 months	
		%	p	%	p	%	p
Medial Femur	**MF**	1.27%	0.216	-1.13%	0.320	-2.52%	0.1326
Trimmed, Window Medial Femur	**nwcMF**	-2.75%	0.031	-4.42%	0.006	-6.85%	0.00273
LateralFemur	**LF**	0.11%	0.928	0.41%	0.824	-0.16%	0.93049
Trimmed, Window Lateral Femur	**nwcLF**	-0.81%	0.548	-0.21%	0.882	-0.61%	0.73289
Medial Tibia	**MT**	0.51%	0.607	-0.59%	0.610	-1.16%	0.43608
Trimmed, Window Medial Tibia	**nwMT**	-1.20%	0.407	-3.48%	0.057	-2.90%	0.1213
Lateral Tibia	**LT**	-1.03%	0.448	-2.00%	0.271	-2.48%	0.11562
Trimmed, Window Lateral Tibia	**nwLT**	-2.78%	0.180	-2.87%	0.207	-3.47%	0.1037

Table 1: % Change in average thickness by compartment and by time

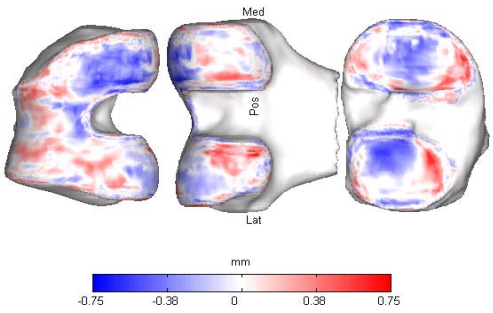

Figure 1: SRM of change at 24 month (blue = loss)

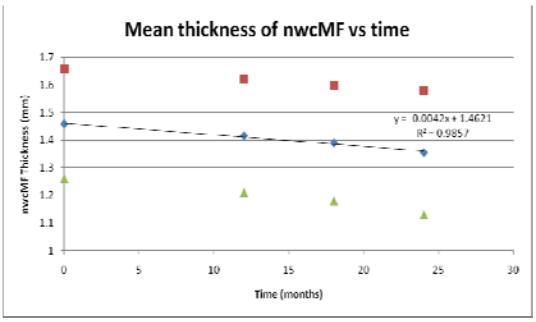

Figure 2: Average nwcMF thickness at 12, 18 and 24 months (showing 95% confidence limits)

CONCLUSION: Loss of articular cartilage in this dataset shows loss in the central medial femur, and in both sides of the tibial plateau. Significant loss was only present in the trimmed, windowed central medial femur region (nwcMF). The change in this region at 6, 12 and 18 months appears to be linear.

SPONSOR: Funded in part by AstraZeneca
DISCLOSURE STATEMENT: None
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ACCURACY OF T1 FITTING FOR PHARMACOKINETIC ANALYSIS OF CONTRAST ENHANCED KNEE MR

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INTRODUCTION: In a recent paper MR pharmacokinetic (PK) modelling of patellar cartilage was shown to differentiate between normal and pathological cartilage by analysis of dynamic scans during the first 3 minutes after administration of intravenous contrast agent (CA) (Sanz-Requena et al JMRI (2008) vol. 27 (1)). For PK analysis contrast curves are calculated based on the measured enhancement, the relaxivity of the contrast agent, and the pre-contrast T1. The varying flip angle method (VFA) calculates a T1-map using a series of spoiled gradient (SG) scans with varying flip angles. T1 values are calculated by fitting to the signal equation. Alternatively, a post-contrast scan may be used to calculate T1 values. The CA shortens the T1 in proportion to the concentration, and results in two effects: signal increases, and the peak signal shifts to larger flip angles. Both effects are potentially beneficial for the accuracy of the T1-fitting procedure, and thus more accurate concentration curves.

OBJECTIVE: Show that in dynamic contrast-enhanced MR studies the accuracy of T1-mapping increases using the VFA method if these are acquired after CA injection.

METHODS: In an ongoing study, knee osteoarthritis patients are included (>50yo). MR scanning is performed on a 3T system (Philips Achieva, Philips Health Care, Best, The Netherlands) using a multi-channel dedicated knee coil. T1-mapping is performed using the VFA method (SG sequence, TR/TE=8/4 ms, flip angles 2, 5, 7, 10, 15, 20, 25, 30, 40 and 60 degrees, 108x108 matrix size, 0.78x0.78 mm pixel size, 2.5 mm slice thickness). CA is administered intravenously (Dotarem, Guerbet, The Netherlands, 0.5 mmol ml^{-1}, r1 = 3.4 L $mmol^{-1}$ s^{-1}), followed by a saline flush (MedRad power injector). T1 scans are made before and after the dynamic acquisition (10 minutes). Analysis is performed using in-house developed software (Matlab, The Mathworks). Using the SG signal equation (S = M0*(1-exp(-TR/T1)*sin(a)/(1-cos(a)*exp(-TR/T1))) curves are generated for T1pre values in the range 100-2000 ms, and for corresponding T1post values in the presence of a range of known contrast agent concentrations (0.01, 0.1, 1, 2 mmol L^{-1}). Normally distributed noise is added to both sets of curves with a standard deviation equal to 10% of the maximum signal of the T1pre value (M0=1 for both). T1 and M0 values are numerically fitted. For each set of T1pre/T1post this procedure is repeated 25 times. ROIs are drawn in the pre and post contrast flip angle scans in homogeneous regions. For each ROI the standard deviation divided by the mean is calculated and the relative enhancement. Pre and post contrast T1 maps are calculated.

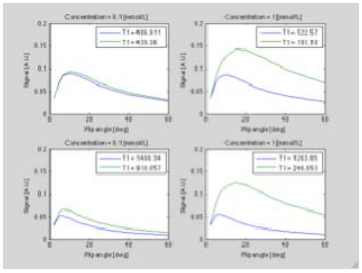

Figure 1: Signal curves

RESULTS:
Fig. 1 shows, for 0.1 and 1.0 mM concentrations of CA and for T1 values of 500 and 1300 ms, the signal generated using the mean of the fitted T1 values. The signal increases and the peak of the signal shifts to larger flip angles. Fig. 2 shows the standard deviation of the fitted T1 values. The standard deviation decreases at higher concentrations of CA. In a patient scan, different regions of the knee show improved SNR corresponding to the concentration of CA: femoral bone marrow 0, subcutaneous fat +10%, and muscle +20%. Fitted T1 values in pre and post contrast scans in ROIs in the same tissues show a decrease in standard deviation which is, depending on the enhancement, varying from no change in bone marrow to a reduction to 30% in muscle and synovial fluid.

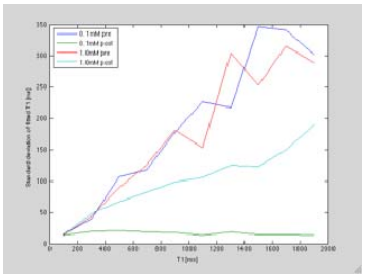

Figure 2: Standard deviation of fitted T1 values.

CONCLUSION: T1-map calculation using the variable flip angle method is more accurate after administering contrast and results in a more accurate estimate of the concentration of the contrast agent.

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ACTIVE APPEARANCE MODELLING OF THE KNEE USING DXA IMAGES

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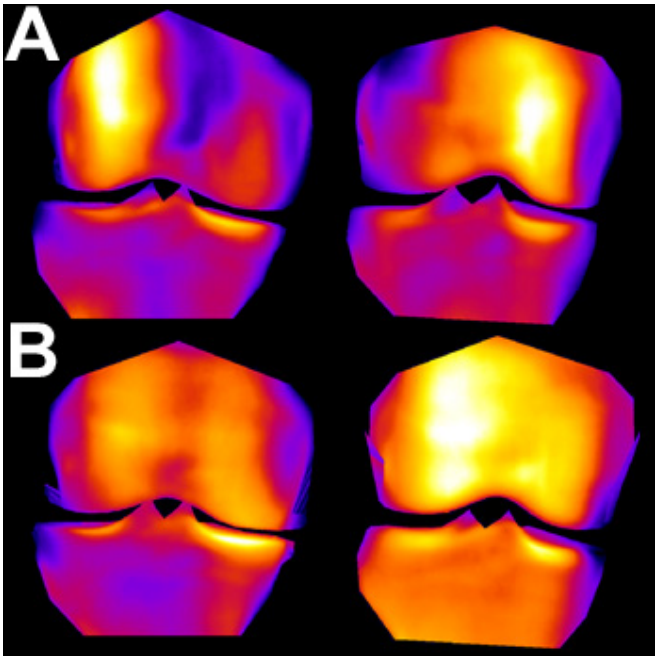
INTRODUCTION: Active Appearance Modelling (AAM) is an extension of Active Shape Modelling (ASM) to include image texture. It uses ASM to define a region of interest and describes the variation of image intensity within its shape in terms of linearly independent modes of variation, found using Principal Components Analysis. We have shown that, when applied to hip radiographs, ASM can identify patients at greatest risk of developing OA and who progress to a total hip replacement (THR) before clinical signs become apparent (1). Dual Energy X-ray Absorptiometry (DXA) images allow quantification of bone mineral density (BMD), and are similar in appearance to radiographs but have lower resolution. We have previously shown that DXA images are of sufficient quality for repeatable KLG scoring and wanted to evaluate their suitability for imaging knee OA combined with an AAM.

OBJECTIVE: To build an active appearance model from DXA images of the knee of volunteers with various degrees of OA severity.

METHODS: The Grampian NHS Radiology Information System was used to identify patients who had had radiographs of both knees taken in the previous 12 months. Knee DXA were obtained in 107 patients, who had agreed to participate in the study: 37 controls (KLG 0 in at least one knee), 24 mild OA (KLG of 1), 22 moderate OA (KLG of 2 in at least 1 knee), and 24 severe OA (KLG of 3 or 4 in at least 1 knee). An AAM was developed from these images.

RESULTS: False coloured images of the first two modes (±2 standard deviations from the mean shape) of the appearance model are shown in the figure. A) Mode 1. Lower scores (left side) were associated with a shallower intercondylar notch, an extended lateral tibial plateau and medial femoral condyle and a shift in femoral BMD distribution to the lateral side. No evidence of osteophytes was noted.



B) Lower mode 2 scores (left side) showed joint space narrowing, a more uneven distribution of BMD, particularly in the tibia, bilateral osteophytes on both the femur and tibia, a wider medial femoral condyle and a shallower intercondylar notch. The lateral tibial plateau is extended beyond the lateral femoral condyle, possibly indicating malalignment.

CONCLUSION: The additive value of using AAM over ASM is highlighted by the identification of areas of sclerosis and variation in BMD distribution in both the femur and tibia indicative of well known anatomical features of OA. Appearance modelling of the knee may be a more sensitive imaging biomarker of OA than shape modelling or KLG alone,

REFERENCE: 1. Gregory JS, et al. Arthritis Rheum 2007;56(11):3634-43.

SPONSOR: This study was supported by an award from the Translational Medicine Research Collaboration.
DISCLOSURE: None
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COMPARISON OF ACTIVE SHAPE AND APPEARANCE MODELLING IN THE RADIOGRAPHIC ASSESSMENT OF HIP OA

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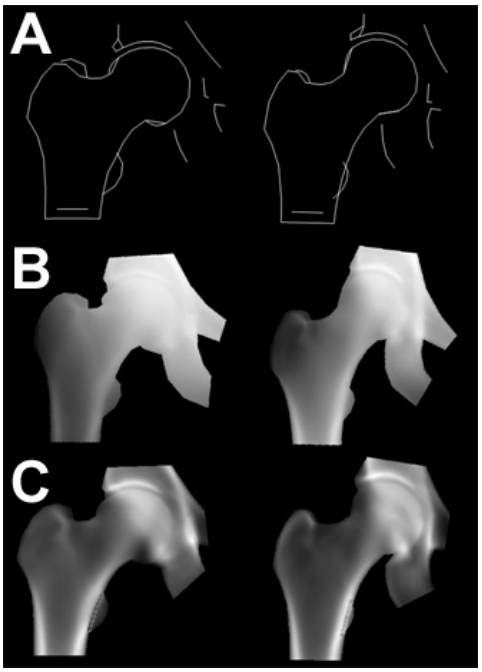
INTRODUCTION: Active Shape Modelling (ASM) has been used by our group to describe the outline of the hip joint through the coordinates of landmark points Principal components analysis applied to ASM of the hip allows sensitive quantification of variation in hip shape characteristic of OA by using a small number of independent variables (modes of variation) (1), Similarly to ASM, Active Appearance Modelling (AAM) uses a shape model to define a region of interest and describes the variation of image intensity within that shape in terms of linearly independent modes of variation. Radiographs are conventionally used in the imaging assessment of hip OA, but Dual Energy X-ray Absorptiometry (DXA) images, which have lower resolution but allow quantification of BMD, may provide a better imaging format for AAM than uncalibrated radiographs.

OBJECTIVE: To compare DXA and radiographs for building ASM and AAM models of hip OA.

METHODS: The Grampian NHS Radiology Information System was used to identify patients who had had radiographs of both hips taken in the previous 12 months. Baseline hip DXA (GE Lunar iDXA) were obtained in 62 patients who agreed to take part in the study, received: 20 mild OA (KLG 0 or 1), 20 moderate OA (KLG of 2 in at least 1 hip), and 22 severe OA (KLG of 3 or 4 in at least 1 hip). A model template, consisting of 85 points describing the outline of the hip and parts of the pelvis (including osteophytes) was developed (Fig). Shape and appearance models were built applying this template to both radiographs and DXA images, and the first mode of variation was visually compared.

RESULTS: The first mode for the three models is shown in the figure. Each row shows ±2 standard deviations from the mean image shape for A) radiograph-ASM, B) radiograph-AAM and C) DXA-AAM. Effective shape models could be built from either DXA or Radiograph images, as changes in the shape of the hip joint were clearly evident. Comparison of the appearance models showed, however, that DXA images were more useful for AAM than radiographs where little textural detail can be seen. The DXA-AAM showed clearly variation in bone structure, particularly between the femoral head and acetabulum and within the femoral neck.



CONCLUSION: Each model and imaging modality has different strengths and weaknesses. ASM is suitable for both DXA and radiographs, though the latter may be preferable due to the higher resolution. AAM however is most suitable for use in DXA images, as the image intensity is standardised.

1. Gregory JS, et al. Early identification of radiographic osteoarthritis of the hip using an active shape model to quantify changes in bone morphometric features: Can hip shape tell us anything about the progression of osteoarthritis? Arthritis Rheum 2007;56(11):3634-43.

SPONSOR: This study was supported by an award from the Translational Medicine Research Collaboration.
DISCLOSURE: None
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HEALTHY MENISCUS PROTECTS AGAINST LOSS OF ARTICULAR CARTILAGE PARTICULARLY IN THE FEMUR

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INTRODUCTION: The integrity and biomechanics of the knee joint are significantly affected by the condition of the meniscus, and it is important to understand the effect of meniscal competence on the progression of patients with osteoarthritis

OBJECTIVE: To determine the spatial and temporal change in cartilage thickness in 3 cohorts of a 12-month progression group of individuals with knee OA, based upon the condition of their medial menisci.

METHODS: A convenience group of 88 individuals (45 male) was identified from the OAI progression group 0.B.1 and 1.B.1. The subjects chosen had K-L scores of 2 or 3; medial JSN greater than lateral JSN, evidence of medial osteophytes and knee alignment of ≥1° of varus mal-alignment measured using the anatomic axis. BMI and varus (average) were for females (32.7, -3.1°) and males (31.3, -3.9°).

Pairs of images were manually segmented using EndPoint software (Imorphics, Manchester, UK), by trained segmenters blinded as to time point, but not to subject. Average thickness (ThCtAB) of the cartilage for each major compartment of the femur and tibia was calculated and loss between the baseline and 12m follow-up assessed using paired t-tests with results expressed as a percentage of the baseline mean. Meniscal scoring was performed by a radiologist using a simplified meniscal scoring system which scored tears as 0:normal, 1:horizontal, 2:vertical, 3:radial, 4: complex and 5:bucket, and for degeneration as 0: normal, 1:minimal, 2:broad rim, 3:thin rim. Meniscal scores were aggregated to give an overall index of meniscal condition of the medial meniscus (min 0, max 20). The subjects were split into 3 groups: Group A had scores of 0-4, Group B 5 – 9, Group C 10-20.

RESULTS:

	Group A (0-4)			Group B (5-9)			Group C (10-20)		
	%	SRM	p	%	SRM	p	%	SRM	p
nwMF	-0.93	-0.156	0.376	-3.48	-0.496	0.008	-4.18	-0.643	0.005
nwMT	-2.15	-0.354	0.048	-3.43	-0.359	0.051	-3.71	-0.510	0.028

Table 1: % Change in average thickness for each of 3 meniscal groups

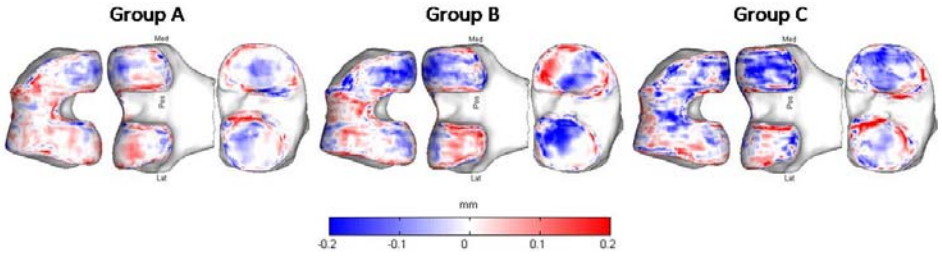

Figure 1: Mean change in each group (mm)

CONCLUSION: The amount of cartilage loss in the medial compartments increased with the amount of meniscal damage. This was particularly true in the femur, where those subjects with the least damage did not lose significant amounts of cartilage, suggesting that a competent meniscus is protective against OA progression. The area affected by loss is also influenced by the condition of the menisci – in groups A and B the loss was confined to the meniscal window in the femur and tibia. In Group C, which represents significant damage, the loss extends outside the area which normally forms the meniscal window.

SPONSOR: Funded in part by AstraZeneca

DISCLOSURE STATEMENT: None

ACKNOWLEDGMENT: Dr David Hunter provided information on the knee alignment and other information for the patient group

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INSIGHTS INTO THE PATHOGENESIS OF PROGRESSIVE ANKLE AND FOOT JOINT DESTRUCTION FROM A MAGNETIC RESONANCE IMAGING STUDY OF CHARCOT'S ARTHROPATHY AND OSTEOARTHRITIS.

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BACKGROUND: Charcot's arthropathy or neuropathic joint disease (NJD) is a particularly severe form of osteoarthritis (OA) that primarily affects the foot and ankle, and typically accompanies diabetes mellitus. Compared to non-NJD ankle and foot OA, NJD is typically rapidly progressive and can lead to permanent disability. In order to better understand the rapidly progressive OA in NJD, we undertook a magnetic resonance (MR) imaging study comparing NJD to non NJD ankle and foot OA.

METHODS: Closely matched foot and ankle cases of NJD (n=8) and OA (n=15) with MR imaging studies were collated retrospectively. The selection of NJD cases was based upon early disease (median duration 3 months and radiographic score of 2 or less). All images included T1 weighted and T2 Fat suppression techniques. Images were scored blindly by a musculoskeletal radiologist for features associated with joint degeneration and trauma including fractures, joint debris, cartilage defects, bone marrow oedema, cyst formation, joint effusions, tendon and ligament damage

RESULTS: Both groups with joint diseases occurred after middle age with similar presentations at consultation. A history of trauma and pain was present in both groups; more often in the OA group than the NJD group. In general, NJD was associated with a greater degree of abnormality in a larger number of bones (see table). The major difference between foot and ankle OA and NJD was the degree of bone oedema, number of bone fractures and debris found in virtually all cases of NJD. Likewise, ligament abnormalities were greater in the NJD group. Regions of focal bone marrow oedema, subchondral cysts and cartilage defects were common to both groups but joint effusions were greater in NJD.

A summary of abnormal magnetic resonance imaging features per group.

Number of abnormal MRI features per group	NJD (n=8) Median (IQR)	OA (n=15) Median (IQR)	Difference	Significance (p=<0.01)
Abnormal Bones	10(5.8)	5(4)	5	p=0.016
Subchondral cysts	2.5(5.8)	2(2)	0.5	p=0.825
Focal BME	3(1.8)	4(3)	1	p=0.428
Diffuse BME	6.5(5.5)	2(5)	4.5	p=0.005
Joint Effusion	7(6.5)	3(3)	4	p=0.047
Fractures	4(8)	0(0)	3.5	p=0.001
Ligament Abnormalities	3(6.3)	0(0)	3	p=0.005
Tendon Abnormalities	0.5(1.8)	0(0)	0.5	p=0.087
Joint Debris	4.5(6.5)	0(0)	4.5	p=0.013
Cartilage Defects	11(5)	5(2)	6	p=0.213

*BME = Bone Marrow Oedema

CONCLUSIONS: This is the first blinded analysis of early NJD compared to non NJD OA. These initial observations show extensive ligament and bone damage near clinical presentation of NJD; typically these findings are seen late in non-NJD OA. Rapidly progressive OA in the NJD setting was intimately associated with bone and ligament damage. These findings suggest the importance of structures other than cartilage in rapidly progressive joint failure in OA. These preliminary findings have implications for future research and therapeutic development.

SPONSOR: None
DICLOSURE STATEMENT: none
ACKNOWLEDGMENT: Dr Elizabeth Hensor is to be thanked for statistical assistance.
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EXAMINING THE PAINFUL OA KNEE JOINT: CLINICAL EXAMINATION FINDINGS AND CORRELATION WITH MAGNETIC RESONANCE IMAGING ABNORMALITIES.

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Introduction: Multiple examination findings are common when examining the painful osteoarthritic (OA) knee joint. Whilst both clinical findings and magnetic resonance (MR) abnormalities have been correlated with symptoms, there is little literature attempting to correlate examination findings with abnormalities noted on MR imaging.

Objectives: To examine the relationship between specific examination findings and abnormalities on contrast-enhanced MR imaging of the painful OA knee.

Methods: 130 patients, 64 (52%) women, mean (SD, range) age 63 (8, 36-83) with ACR OA knee and varying degrees of pain were enrolled in this cross-sectional study.
Detailed clinical examination of the most painful knee was recorded by the same assessor for all subjects, prior to MR imaging using a 1.5 Tesla Philips system dedicated quadrature knee coil, with gadolinium contrast. Imaging was performed within 48 hours of clinical examination. Axial and coronal T1 weighted spin echo, sagittal proton density spin echo and sagittal T2 3D gradient echo with spectral fat suppression sequences were performed pre-contrast and a spoiled gradient echo T1 weighted sequence and repeat axial and coronal T1 sequences post-contrast. All MR images were scored by an experienced musculoskeletal radiologist using the Boston-Leeds Osteoarthritis Knee Score (BLOKS). As the majority of subjects felt that the medial aspect of their knee was most painful and the medial compartment also generally showed more damage, we focused on this area to examine structural associations. Logistic regression models controlling for BMI and disease duration were used to identify medial compartment pathology scores that were associated with specific MR imaging abnormalities.

Results: Clinical findings were common in the painful OA knees of this secondary care cohort. Half of those examined had a joint effusion (30% minimal and 20% moderate) and around half had abnormal knee joint alignment (44%) with 32% varus and 12% valgus. Few had features of general hypermobility (3 subjects) or abnormal knee hyperextension (4 subjects).
80% demonstrated medial joint line tenderness and 50% lateral joint line tenderness. Medial joint line tenderness (OR 2.38, p=0.101) and pain through motion (OR=3.23, p=0.023) were positively correlated with medial synovitis. A third demonstrated medial or lateral compartment crepitus and two-thirds (68.5%) patellofemoral crepitus. Medial compartment crepitus correlated with full thickness medial cartilage loss (OR=2.18, p=0.054). There was also a significant correlation between medial knee pain at end of range of movement and MR findings of >75% area cartilage loss, >75% thickness of cartilage loss, full thickness cartilage loss and medial meniscal maceration (all $p<0.05$).

Discussion: This is the first study that has demonstrated the imaging significance of specific clinical findings. Crepitus may represent full thickness cartilage loss. Cartilage loss may also contribute to knee pain through motion and pain on stressing the medial ligament. Synovitis has been previously associated with knee pain and is here suggested as a contributor to both medial joint line tenderness and medial pain through motion.

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Disclosures: None
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DO BASELINE SYNOVITIS AND EFFUSION PREDICT STRUCTURAL PROGRESSION IN SUBJECTS WITH EARLY OR PRE-OA? – THE MOST STUDY

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INTRODUCTION: Synovitis and effusion are frequently present in OA and correlate with pain and other clinical outcomes. Semi-quantitative measures of synovitis from Hoffa's fat pad are associated with pain severity and similarly change in synovitis is associated with change in pain severity. If synovitis in OA appears to predispose to further structural progression has been questioned, although high grade synovitis seems to play a role in structural deterioration. This is consistent with theories suggesting that synovitis present in OA is triggered by cartilage detritus, which stimulates activation of synoviocytes and thus seems to be a secondary phenomenon. However, the clinical data supporting this theory is limited. Synovial inflammation does appear to occur in early OA, but as to whether it occurs prior to damage to other tissues remains unclear.

OBJECTIVE: Aim of the study was to assess if presence of baseline synovitis and effusion in knees without or pre-OA, predicts future cartilage loss.

METHODS: The Multicenter Osteoarthritis (MOST) Study is a longitudinal observational study including subjects with OA or at risk of developing it. All subjects without radiographic OA (Kellgren-Lawrence grades 0 and 1) and available BL and 30-months follow-up (FU) MRIs were included. MRI was performed at a 1.0 T extremity system. MRIs were assessed semiquantitatively according to the WORMS scoring system (FWR, AG, MDC). Only knees with no TF cartilage damage as defined by MRI were included. A synovitis-surrogate of signal changes in Hoffa's fat pad was scored from 0-3 in the infrapatellar and intercondylar subregions and effusion was scored from 0-3 according to the amount of joint distension. Definite synovitis was defined as any grade ≥2 and definite effusion as any grade ≥2. Knees with scores of either 0 or 1 were the reference. Logistic regression was used to estimate the risk of cartilage loss at 30 months. Adjustment was performed for possible confounders of future cartilage damage, i.e. baseline effusion, synovitis, patello-femoral cartilage damage, meniscus damage, meniscal extrusion, BMI, age, gender, malalignment, bone marrow lesions.

RESULTS: 514 knees (1 knee per patient) were included. 43 knees showed definite synovitis, and 53 presented with definite joint effusion. After adjustment, baseline synovitis was not associated with an increased risk of cartilage loss at follow-up (adjusted odds ratio 1.0 [95% confidence intervals 0.5-21, p=0.89]). Knees with baseline effusion had an increased risk for cartilage loss (adjusted odds ratio 2.7 [95% confidence intervals 1.4-5.1, p=0.002]).

CONCLUSION: Baseline synovitis does not predict cartilage loss, but joint effusion. The non-specific surrogate used for synovitic assessment might not be ideal for assessment in longitudinal studies and contrast-enhanced MRI might yield different results. Baseline effusion as a reflection of synovial activation seems to play a role predicting structural progression in early or pre-OA.

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A COMPARISON OF FAT-SUPPRESSED INTERMEDIATE WEIGHTED FAST SPIN ECHO (IW) AND DOUBLE ECHO STEADY STATE (DESS) SEQUENCES FOR SEMIQUANTITATIVE ASSESSMENT OF FOCAL CARTILAGE DAMAGE AT 3 T MRI: THE JOG STUDY

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INTRODUCTION:
Modern MRI systems offer a multitude of cartilage-dedicated sequences which are being used clinically and for research purposes applying quantitative cartilage morphometry. It is unknown if these dedicated sequences are equally useful for semiquantitative scoring of focal cartilage defects.

OBJECTIVE:
The aim of the study was to compare semiquantitative assessment of focal cartilage damage using the DESS- and IW-sequences at 3 T MRI.

METHODS:
The JOG-study includes 177 subjects aged 35-65 with frequent knee pain. 3 T MRI of both knees was performed at baseline with a comparable pulse sequence protocol as applied in the Osteoarthritis Initiative (OAI): sagittal IW 2D TSE FS, sagittal 3D DESS WE, axial MPR of SAG 3D DESS WE, coronal MPR of SAG 3D DESS WE. Cartilage status was scored on a scale from 0-6 according to the Whole Organ Magnetic Resonance Imaging Score (WORMS) system by one experienced MSK radiologist (FWR) taking into account all five sequences. A total of 245 superficial (WORMS 2.0 lesions) or full-thickness defects (WORMS 2.5 lesions) were detected. In an additional consensus reading by two MSK radiologists (FWR, AG), the lesions were evaluated side-by-side using only the sagittal 3D DESS WE - and sagittal IW 2D TSE FS -sequences. Lesion conspicuity was graded from 0-3, hyper-and hypointensity signal changes adjacent to the defect were recorded as present or absent and sequence that depicted the lesion with larger maximum diameter was recorded for each cartilage defect. Wilcoxon statistics were applied to determine differences between the sequences.

RESULTS:
37 (17.5%) of the scorable lesions were located in the medial tibio-femoral (TF), 47 (22.8%) in the lateral TF and 126 (59.7%) in the patello-femoral compartment. 82.5% were superficial and 17.5%full-thickness defects. Conspicuity was superior for the IW-sequence ($P<0.001$). The DESS-sequence showed more associated signal changes ($p<0.001$). In 37 (17.5%) cases, the DESS sequence showed the lesions as being larger (in direct comparison to IW); in 71 cases (33.6%), both sequences depicted lesion with the same size and in 103 (48.8%) cases, the IW showed the lesion as being larger ($p<0.001$).

CONCLUSION:
The cartilage-dedicated DESS-sequence was inferior to the IW sequence in depicting the number and size of focal cartilage defects. More intrachondral signal changes were observed with the DESS, but the significance of this finding is unclear.
Semiquantitative assessment of focal cartilage defects should not only be performed on cartilage-dedicated sequences but also on conventional fat suppressed fast spin echo sequences. This might be especially relevant for future assessment of OAI image data as the sequence protocol and MRI system used in the JOG study were comparable.

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DISCLOSURE STATEMENT: Frank Roemer, Ali Guermazi and Michel Crema are shareholders of Boston Imaging Core Lab, LLC, a company providing radiological image assessment services. Ali Guermazi is shareholder of Synarc, Inc. None of the other authors disclose any possible conflict of interest.

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AUTOMATED ATLAS BASED SEGMENTATION OF KNEE MR IMAGES; REPRODUCIBILITY AND REPEATABILITY OF SIGNAL MEASUREMENTS IN OSTEOARTHRITIS PILOT DATA

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STATEMENT OF PURPOSE: In addition to eventual cartilage loss, osteoarthritis of the knee causes changes in other structures, including bone marrow lesions, joint fluid, synovial thickening, Hoffa's fat pad inflammation etc. Even as most studies have focused on cartilage, there is increasing evidence that cartilage loss is preceded by or accompanied with other changes in cartilage, and changes in bone and other soft tissues. However, the causal relationship is not well understood. All scoring systems developed to evaluate non-cartilage changes are based in the change in the structure's signal intensity behavior as compared to a normal. The changes in signal intensity of the structure reflect changes in either its composition or inner architecture.
Preliminary data have shown that cartilage signal behavior separates normals from early OA. There is also evidence that subchondral bone and calcified cartilage vascularize before cartilage loss and that calcified cartilage advances into non-calcified cartilage in the early phase of the disease. All of these phenomena change the signal intensity of the cartilage and the underlining bone. Analyzing these events in longitudinal image data would advance our understanding of the disease pathophysiology. The Osteoarthritis Initiative (OAI) has collected a large amount of clinical information about knee OA including MIR image data. However, due to the time and cost requirements related to the image analysis and scoring, most of that image data are not yet analyzed.
An automated, time efficient approach with minimal human intervention would make a large scale analysis of that data practical and economically feasible. Therefore we developed a fully automated, atlas based segmentation and analysis system to segment and analyze bones, cartilage and anatomic regions from knee MR image data. Here we compare the performance of the automated system and an expert radiologist for repeatability and reproducibility. Measurements included the average signal intensity of cartilage, its deep layer, and the superficial layer of underlying bone for medial and lateral tibia regions, medial and lateral central femur regions. Further, for signal intensities affected by possible soft tissue inflammation, meniscus changes or joint fluid in lateral and medial weight bearing regions of the knee, we evaluate the repeatability and reproducibility of the average signal intensity measurements for those regions.

METHODS: The atlas for the automated system was created by manually tracing five subjects' 3D DESS images from the 0.D1Osteoarthritis Initiative public use dataset and selecting the best performing atlas for further refinement. The resulting atlas was used for this study. The repeatability study consisted of 30 randomly selected and anonymized subjects' 3D DESS images from the 0.D.1, 1.D.1, and 2.D.1 subset of the Osteoarthritis Initiative public use dataset. Of these, 10 were randomly selected and anonymized creating 40 blinded images for manual and automated segmentation . The automated segmentations were performed five times with varying initial parameters. The final measurements were obtained by trimming the highest and lowest values and averaging the three remaining measurements. The reproducibility part consisted of 38 anonymized sagittal 3D DESS image sets of 19 subjects' scan-rescan studies from the OAI pilot study. These were segmented both semi-manually and automatically. The automated measurements were generated with a trimmed average of five segmentations using varying initial parameters.
The following parameters were automatically calculated for medial and lateral tibial and femoral cartilage regions: average signal intensity of the cartilage; that of the deep layer of the cartilage and that of the superficial layer of subchondral bone. Further, the average signal intensity of medial and lateral inter-bone regions, (the three dimensional presentation of joint space seen in plain films) was automatically calculated. The reproducibility was calculated by computing mean-square (RSM) coefficient of variation (CV%) for each parameter .

RESULTS: In the repeatability study, the automated segmentation produced identical results for all measured parameters. The CV for the manual approach varied between 2.3%-10%. The scan-rescan reproducibility for the automated method varied from 1.75% for the average signal of the lateral femur central (weight bearing) cartilage to 3.01% for the average signal of the deep layer of the lateral tibia cartilage. The average signal intensities of the cartilage plates varied being generally lower for the tibia cartilage plates, (averaging 198 for lateral tibia cartilage) than for the femur, (averaging 224 for the lateral femur cartilage). The signal intensity of the deep layer of the cartilage varied from 96 to 201, being higher for femur than for tibia. The average signal intensity of the superficial layer of the subchondral bone was considerably lower for all areas; the average for lateral tibia being 89 compared to 99 of the lateral femur. The reproducibility for inter-bone, 3D joint space signal intensity was 2.34% for lateral and 1.57 % for medial inter-bone regions using automated tools compared to 3.42 % and 3.34 % for manually edited regions.

CONCLUSION: The automated atlas based MR image analysis system used in this study to segment the knee into bones and cartilage, and divide the joint in regions and in sub-segments provided repeatable and highly reproducible signal intensity measurements in the medial and lateral weight bearing regions of the knee. These automated tools provide a realistic opportunity to characterize the behavior of structural and compositional changes in cartilage and non-cartilage tissues in OA by analyzing larger populations such as the OAI or other longitudinal datasets.

CARTILAGE-BONE CONTRAST BEHAVIOR IN OAI PROGRESSION SUB-COHORT; CORRELATION TO WOMAC SCORES

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STATEMENT OF PURPOSE: OA involves all components of the joint including the bones, ligaments, cartilage, menisci, periarticular fat, synovium and muscles. Despite extensive studies, the temporal relationship between changes related to OA in different structures and the clinical symptoms are not very well understood. Relatively few MR imaging studies have correlated imaging findings to present pain and even fewer to future knee pain as a predictive biomarker. Identification of biomarkers that are indicators of asymptomatic preclinical disease or that will predict the symptomatic stage of the disease would have significant impact on the development of disease prevention approaches. However, the time, effort and resultant cost of segmentation have prevented attempts to capture a variety of possible indicators for comparison to clinical findings. To investigate the feasibility of a more efficient approach, we utilized a fully-automated quantitative analysis method using the CiPAS© software (José G Tamez-Peña, Monterrey, México) to segment and analyze bones, cartilage and anatomic regions from knee MR image data. Previous work has shown that this method is repeatable and highly reproducible for regions' and structures' signal intensity measurements. In this initial study of 150 subjects' baseline and 1 year scans from the Osteoarthritis Initiative (OAI) progression cohort, we compared the K&L OA grade and total WOMAC score to the signal contrast at the bone-cartilage interface in the central regions of the medial and lateral compartments and the trochlea.

METHODS: This study's 150 subjects were from OAI Progression sub-cohort public use datasets 0.B.1 and 1.B.1. The 150 subjects' target knees' sagittal 3D DESS WE sequence (baseline, 1YR) and total WOMAC scores and K&L grades were used for this study. The images were first segmented using an automated, atlas-based method into knee bones, cartilage and anatomic regions. Signal intensities for the deep layer of cartilage and the superficial layer of bone were used to calculate the contrast at the bone-cartilage interface for medial and lateral weight bearing regions of the tibia and femur. The contrast measurements were compared to the OA grade and total WOMAC score. Regressions models were used to study the association of the contrast measurements to the WOMAC and KL scores. Image pairs that did not pass the QC were excluded from the analysis.

RESULTS: Cartilage-bone signal contrast at the central femur regions were associated to the KL scores (cMF: r=0.40, p<0.001; cLF: r=0.24, p=0.002). At baseline, the signal contrast correlated weakly with WOMAC scores in the medial weight bearing area of femur (cMF: r=0.21, p=0.007). Figure 1 shows the box plots at three OA grades of the contrast at the cMF and the cLF (medial, lateral weight bearing region of femur). Figure 2 right, shows the scatter plot of the baseline WOMAC to the model: WOMAC= cMF+cLF+MT+LT+Tr+MJS+LJS.

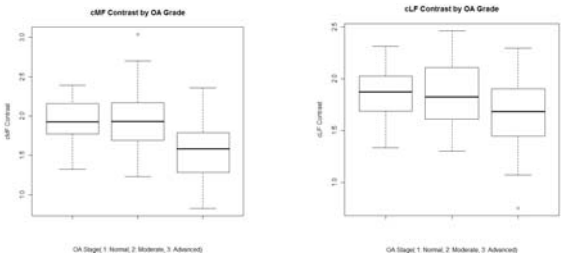

Figure 1. Box plots of the contrast at three OA grades(Normal: KL<2, Moderate: KL=2 and Advanced: KL>2).

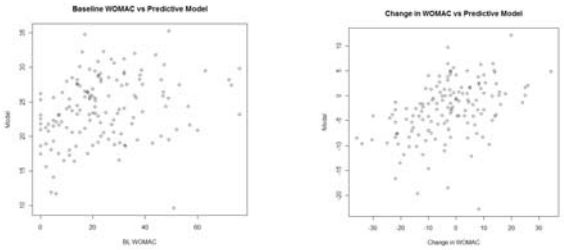

Figure 2. Left, Scatter plot of the model: WOMAC = cMF + cLF +MT +LT +Tr +MJS+LJS vs the baseline WOMAC scores. Right, the scatter plot of the model: WomacChange=BLWOMAC+cMF+TIME to change between Baseline and the one year follow up in WOMAC socres.

Finally, the change in cLF showed an association to the change in the total WOMAC ($r=0.26$, $p<0.001$). Figure 2 left, shows the scatter plot of the change in WOMAC to the predictive model WomacChange=BLWOMAC +cMF+TIME ($r=0.42$, $p<0.001$). The study, including segmentation of 300 individual MRI HR DESS images was conducted over 43 calendar days.

CONCLUSIONS: This study evaluated the feasibility of automated atlas based segmentation and analysis method to evaluate the cartilage-bone contrast biomarkers and their relation to the present and future clinical symptoms. In this study the cartilage-bone contrast in central femur at baseline was associated with the WOMAC scores and changes in signal at the cLF predicted change in the WOMAC scores. The correlation of signal contrast with disease state and progression is consistent with published literature describing pathophysiological changes, including vascularization of the tidemark, breakdown of collagen, and inflammation, all of which tend to increase water content, and thus affect MRI signal. Although the sample size of this study (n=150) was significant from the standpoint of time and resources traditionally necessary to analyze image data, it is still small with regard to the number of individual measurements potentially derivable from segmented MRI scan data, and the population sizes if broken down by gender, baseline OA grade or other sub-categorization. However, this study indicates that with the automated system the new potential biomarkers' behavior and their relation to the clinical symptoms can be tested in a reasonable time frame with much larger data sets.

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POSSIBLE CAUSES OF DISCREPANCIES BETWEEN X-RAY DETECTED JOINT SPACE NARROWING AND SEMIQUANTITATIVELY ASSESSED CARTILAGE LOSS ON MRI IN THE MEDIAL TIBIOFEMORAL JOINT: DATA FROM THE OSTEOARTHRITIS INITIATIVE

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INTRODUCTION: Radiographic JSN is commonly used to assess disease progression in TF OA. Radiographic joint space width is an indirect reflection of cartilage integrity and other joint structures such as the menisci. Direct visualization of cartilage and non-osseous joint tissues is only possible by MRI. Disagreement between radiographic and MRI assessment of progressive cartilage loss may be observed and several reasons for this disagreement are possible.

OBJECTIVE: Aim of the study was to describe agreement and disagreement between medial TF compartment progression over 24 months assessed by radiographic JSN and semiquantitative MRI assessment of cartilage loss using the BLOKS and WORMS semiquantitative scoring systems in a sample of knees from the Osteoarthritis Initiative (OAI).

METHODS: 50 knees of participants with frequent pain, radiographic OA and risk factors for progression were studied. Baseline and 24-months fixed-flexion radiographs were read paired but blinded to order by two readers (with adjudication of discrepancies) for medial TF JSN using the OARSI grades. Increases in JSN>0 were considered progression. On MRI, cartilage morphology was scored semiquantitatively using both WORMS and BLOKS systems for baseline and 24-months visits. For both, radiographic OARSI JSN assessment and WORMS cartilage scoring, readers recorded definite within-grade changes that did not meet criteria for a full grade change. MRI images were read paired, but blinded to time order, by two experienced radiologists. Inter-observer reliability for cartilage lesion scores was 0.88 (w-kappa) for WORMS and 0.75 (w-kappa) for BLOKS (lesion extent). A knee with an increase of >0 in either the cartilage lesion extent-dimension or the cartilage thickness-dimension in either the tibial or femoral weight-bearing subregion was considered as medial TF cartilage loss in BLOKS readings. A knee with an increase in cartilage morphology scores of >0 in any of the three tibial and the central and posterior femoral subregions was considered as medial TF cartilage loss in WORMS readings. Knees with discrepancies between X-ray and MRI readings were reviewed in consensus for possible explanations.

RESULTS: 7 knees had a baseline JSN score of 3 and could not progress; none of these showed any worsening by MRI. 10 of the remaining 43 (23%) knees showed JSN progression; of these, 5 (50%) had no cartilage loss by either WORMS or BLOKS, 3 (30%) progressed by both systems and 2 progressed by WORMS only. 33/43 (77%) knees had no JSN progression; of these, 7 (21%) had cartilage loss on MRI. 5/43 knees progressed using the BLOKS system (2/5 did not progress by JSN) and 11 progressed using WORMS (6/11 did not progress by JSN). 31/43 knees had no cartilage loss by either system; 5 of these had JSN progression but none exhibited worsening meniscal damage or extrusion.

CONCLUSIONS: Disagreement between longitudinal X-ray scoring and semiquantitative MRI assessment of cartilage in the medial TF compartment is not rare. For the knees, that showed progressive JSN and no progression on MRI, ceiling effects of both MRI scoring systems for meniscal assessment need to be considered. In addition incident susceptibility artifacts on MRI probably due to calcifications within the joint space were also observed and may explain disagreement. Positioning inconsistency may further explain some of the JSN progression without concomitant MRI progression or insensitivity to change on X-ray when MRI progression was seen. Worsening in MRI cartilage morphology but no progression on X-ray appear to reflect progressive cartilage loss in the posterior femur and increase in size of focal defects only detectable on MRI.

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CENTRAL VS. CLINIC READING OF KNEE RADIOGRAPHS FOR BASELINE OA IN THE OSTEO-ARTHRITIS INITIATIVE PROGRESSION COHORT: IMPLICATIONS FOR PUBLIC DATA USERS

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INTRODUCTION: Studies of knee OA often use a decentralized, clinic-based x-ray reading to screen for OA status and eligibility. Central reading of the x-rays may disagree on OA status compared screening readings, with implications for sample stratification and analysis.

OBJECTIVE: To compare baseline knee OA status from central reading of OAI knee x-rays with that from the clinic screening readings.

METHODS: Baseline bilateral PA fixed-flexion knee x-rays were read by one of multiple readers at each the 5 OAI clinics for definite (OARSI atlas grade ≥1) osteophytes (OST) and joint space narrowing (JSN). Clinic readers were trained centrally by teleconference and certified for agreement with standard examples of OST and JSN using a web-based program. Early in recruitment a sample of clinic readings was reviewed centrally by a musculoskeletal radiologist and feedback given on discrepancies. Subjects with an OST and frequent pain in the same knee were assigned to the Progression cohort. As part of an ongoing central reading for progression, baseline knee x-rays of 624 of 1,389 Progression cohort subjects have each been read by 2 expert readers for Kellgren-Lawrence grade (KLG). Disagreements were adjudicated by a panel of 3 readers (including the first 2) with a requirement that 2 of 3 agree on presence/absence of OA, defined as KLG≥2 (presence of a definite OST). Knees were assigned KLG=1 when the presence of osteophytes was uncertain.

RESULTS: 25% of knees with OA (definite OST) by clinic reading had KLG<2 by central reading; nearly half of these were KLG=1. For knees with OST and JSN by clinic reading, 87% had a KLG≥2, while 53% of knees with OST and no JSN by clinic had OA by the central reading. Based on the central reading, an estimated 17% of subjects in the Progression cohort have KLG<2 in both knees, 8% are bilateral KLG=0, and 18% do not have symptomatic OA (KLG≥2 and frequent pain) in either knee.

Table. OA status of knees by clinic reading: N (%) with KLG

Central Reading	No Definite OST (N=210)	Definite OST, No JSN (N=357)	Definite OST and JSN (N=675)	All knees with definite OST (N=1032)
KLG = 0	94 (44.8%)	108 (30.3%)	28 (4.1%)	136 (13.2%)
KLG = 1	57 (27.1%)	61 (17.1%)	58 (8.6%)	119 (11.5%)
KLG ≥ 2	59 (28.1%)	188 (52.6%)	589 (87.3%)	777 (75.3%)

CONCLUSIONS: OAI screening readings and central reading often disagree on baseline knee OA status, suggesting different thresholds for, or interpretation of, definite OST. Analyses of OAI data requiring knees with a high specificity for definite radiographic OA should select those with OST+JSN by clinic reading or, when central a reading is available, KLG≥2.

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JOINT DISTRACTION AS TREATMENT OF END STAGE OSTEOARTHRITIS LEADS WITHIN ONE YEAR TO STRUCTURAL CARTILAGE REPAIR AS EVALUATED BY MRI AND X-RAY

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PURPOSE Progressive prolonged clinical efficacy of joint distraction in the treatment of severe ankle and hip osteoarthritis has been reported. The present study describes the first results on structural repair in case of joint distraction in the treatment of severe knee osteoarthritis.

METHODS Relatively young patients (<60 yrs) with severe osteoarthritis of the tibio-femoral joint, who were considered for an endoprosthesis were treated with joint distraction. An external fixation frame (with springs) bridging the knee joint was placed, distracting the joint 5 mm for a period of two months. Intermittent intra-articular fluid pressure in combination with an absence of mechanical stress on the cartilage, and changes in peri-articular bone turnover during distraction are considered causative for structural repair. In addition to pain, functional disability and clinical condition of the joint, structural changes were evaluated by standardized X-rays analyzed digitally by KIDA software[1] and by quantitative MRI analysis[2].

RESULTS Ten patients (50± 2 yrs) with severe knee osteoarthritis treated with joint distraction have reached one year of follow-up thus far. One year after distraction, VAS pain, very high before treatment for all 10 patients (71± 2% of the maximum score) had decreased significantly to 33± 8%. The WOMAC (50± 5% at baseline) increased significantly to 72± 5% of the maximum score. Clinical condition was poor before treatment, 46± 4% of the maximum score, and increased significantly to 80± 7%. Radiographic evaluation demonstrated a clear increase in JSW (see table). Most importantly, MRI evaluation demonstrated a significant increase in cartilage area and thickness (see table).

			mean	SEM	*p*=	mean	SEM	*p*=	mean	SEM	*p*=	mean	SEM	*p*=
	n=10; 1 yr post treatment													
X-ray	minimum JSW	Δmm	1.20	0.42	*0.022*									
						medial						lateral		
	mean JSW	Δmm	1.05	0.42	*0.074*				0.40	0.59	*ns*			
				Tibia			Femur			Tibia			Femur	
MRI	cartilage volume	Δmm^3	256.7	59.4	*0.009*	298.4	55.3	*0.007*	-14.9	20.0	*ns*	51.8	13.5	*0.028*
	cartilagethickness	Δmm	0.20	0.05	*0.022*	0.47	0.08	*0.007*	-0.02	0.02	*ns*	0.06	0.02	*0.047*
	cartilage coverd bone	Δcm^2	1.76	0.40	*0.009*	1.84	0.40	*0.009*	0.00	0.04	*ns*	0.10	0.04	*ns*
	percentage denuded bone	Δ%	-13.08	3.28	*0.021*	-28.59	5.76	*0.012*	0.12	0.09	*ns*	-0.17	0.23	*ns*

CONCLUSIONS Clinical efficacy of distraction in case of severe knee osteoarthritis was surprisingly quick and good (almost complete normalization in 12 months) and lasted for at least 4 years now (data not shown). JSW widening on X-rays and an increase in cartilage covered area and thickness on MRI suggest actual repair of cartilage. This is to our knowledge the first treatment that clearly demonstrates cartilage regeneration at an astonishing rate. Longer follow-up with more patients is definitely warranted.

[1]Marijnissen et al, Osteoarthritis & Cartilage 2008

[2] Burgkart et al. Arthritis & Rheumatism 2001

REPRODUCIBILITY OF SEMI-AUTOMATED SEGMENTATION AND VOLUME MEASUREMENT OF KNEE CARTILAGE FROM OAI MR IMAGES

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INTRODUCTION: High-resolution MR imaging of knees such within the OAI dataset has the potential to produce a wealth of information, but quantitative measurement of cartilage volume and thickness requires segmentation of the cartilage region from the surrounding tissue. Since cartilage segmentation is a laborious and time consuming process, there is a critical need for more efficient cartilage segmentation procedures. Recently, graph-cuts algorithms have been suggested as solutions to a wide range of image processing problems including segmentation.

OBJECTIVE: To assess the intra- and inter-observer reproducibility of a semi-automated segmentation method based on a graph-cuts algorithm for volumetric measurements of the cartilage from high-resolution knee (3Tesla) MR images.

METHODS: Twenty baseline double-echo and steady-state (DESS) knee MR images in the OAI database (0.B.1 Imaging Data set) were selected to represent varying Kellgren-Lawrence (KL) grades (from 0-4) on fixed flexion knee radiographs. Two trained radiologists independently used the semi-automated method to segment knee cartilage and generate cartilage volumes. Both performed the procedures twice for each participant. The intra-and inter-observer reproducibility of the segmented cartilage volumes were determined by the coefficient of variation (CV%). The results were also stratified into low- and high-KL groups (KL 0-1 vs. 2-4). T-tests were used to evaluate the differences in cartilage volume measurements and CV% within and between the observers.

RESULTS: The mean (±SD) intra-observer CV% for the 20 cases was 1.29 (±1.05)% for observer 1 and 1.67 (±1.14)% for observer 2, while the mean (±SD) inter-observer CV% was 1.31 (±1.26)% for session 1 and 1.79 (±1.72)% for session 2. There was no significant difference between the two intra-observer CV%'s (*P*=0.272) or between the two inter-observer CV%'s (P=0.353). The mean intra-observer CV% of the low-KL group was significantly smaller than that for the high-KL group for observer 1 (0.83% vs 1.86%: P=0.025), but both were still excellent. A significant difference in segmentation processing times between the two observers was noted, mean 49±12 vs 33±6 min for session 1 and 49±8 vs 32±8 min for session 2 for observer 1 vs. 2 respectively

CONCLUSION: We have demonstrated high intra- and inter-observer reproducibility with use of the semi-automated graph-cuts method for cartilage segmentation and volume determination from high-resolution 3T MR images of the knee in participants with varying severity of radiographic OA.

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QUANTIFICATION OF CARTILAGE LOSS IN LOCAL REGIONS OF KNEE JOINTS USING SEMI-AUTOMATES SEGMENTATION SOFTWARE: ANALYSIS OF THE LONGITUDINAL DATA FROM THE OSTEOARTHRITIS INITIATIVE (OAI)

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INTRODUCTION: Quantitative cartilage morphometry is a valuable tool to assess OA progression, however we believe that these methods are not fully exploited when measures of total or sub region volume are used.

OBJECTIVE: We conducted a study to examine change in cartilage morphometry longitudinally. This abstract describes the evaluation of a semi-automated cartilage segmentation software tool capable of quantifying cartilage loss in a local indexed region.

METHODS: In this study we examined the baseline and 24 months follow up visits of twenty subjects from the Osteoarthritis Initiative (OAI), using the KL score of 3 at baseline as the inclusion criteria. The 3D DESS (sagittal, 0.456 mm x 0.365 mm, 0.7 mm slice thickness, TR 16.5 ms, TE 4.7 ms) images were obtained on a 3-T Siemens Trio MR system. One independent reader (HY) marked a single region of local thinning on a randomly selected time point for each subject. Three additional readers (TI, RB, and AW) segmented the cartilage using the software method. For each subject, segmentation of one 3D-image series was first performed and then the corresponding series were segmented by viewing both image series concurrently in two adjacent windows. The reader could adjust the slice location of the pairs so that approximately matching slices from each data sets were displayed together. The readers were blinded to time point. Each baseline-24 month segmentation pair was then registered in 3D and the change in cartilage volume was measured in a local region.

RESULTS: After 3D registration, the change in cartilage volume was calculated in the vicinity of the marked point. Our study examined the volume change (□V) in four regions: < 5 mm, < 10 mm, and < 20 mm from the marked point and for the entire medial compartment of femur. The responsiveness was quantified using the mean, standard deviation of the change, standardized response mean (SRM) values, and the percentage of subjects that showed a loss in cartilage volume. The results are presented in the following table.

Region	□V (mm^3)	SD (mm^3)	SRM	Percentage
< 5 mm	-10.9	15.9	-0.68	80 % (16/20)
< 10 mm	-48.9	43.1	-1.13	90 % (18/20)
< 20 mm	-97.3	165.5	-0.59	75 % (15/20)
Medial compartment femu	-120.1	366.3	-0.33	70 % (14/20)

Table 8. Results from study of longitudinal cartilage loss. Measurements of cartilage loss

CONCLUSION: The results suggest that measurement of cartilage loss in a local region is superior to larger areas and to the total sub-plate. There also may be an optimal region size (10 mm) in which to measure change. The results support the hypothesis that local region measurement is superior. Furthermore we have also demonstrated that cartilage thinning can be observed using a method where only half of the femur is segmented.

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COMPARISON OF WORMS AND BLOKS SEMI-QUANTITATIVE KNEE MRI SCORING FOR ASSESSING CARTILAGE LOSS: RESULTS FROM THE OSTEOARTHRITS INITIATIVE

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INTRODUCTION: Cartilage lesions in the knee can be graded using semi-quantitative (SQ) methods. Whole Organ MRI Scoring (WORMS) and Boston Leeds Osteoarthritis Knee Scoring (BLOKS) both assess areal extent and depth of cartilage lesion. WORMS uses a single 7 point scale in 14 anatomical subregions. BLOKS uses separate 0-3 scales for extent and depth, each scored in 8 subegions. Such differences between the two methods may affect their relative sensitivities for assessing cartilage loss.

OBJECTIVE: We evaluated inter-reader reliability and relative sensitivities of WORMS and BLOKS as methods for assessing the presence of longitudinal cartilage loss from MRI of the OA knee.

METHODS: We studied 115 knees with frequent pain, radiographic OA and risk factors for cartilage loss, which included baseline JSN (OARSI grade ≥1), malalignment (varus vs. non-varus) assessed from a full-limb radiograph and BMI (per SD increase). Cartilage morphology was scored using WORMS and BLOKS from baseline and 24-month visit knee MRIs. Images were read paired, but blinded to time order, by one of 2 experienced radiologists (FWR, AG). Each read approximately equal numbers of knees. 25 knees received duplicate readings to examine inter-reader reliability. WORMS and BLOKS readings of a knee were separated by at least 2 weeks, and the scoring system used first was randomly ordered.. For both scoring systems we defined whole grade worsening of cartilage as an increase cartilage score (increase >0) in any subregion of a knee (or within the subregions of a specific tibio-femoral compartment, for compartment based analyses). For WORMS, based on experience in previous longitudinal studies, readers recorded when a definite, but "within-grade" change in a subregion occurred as well as recording whole grade changes

RESULTS: Weighted kappas (k) for inter-rater reliability of severity of baseline lesions were 0.88 (WORMS), 0.91 (BLOKS lesion extent), and 0.88 (BLOKS full thickness). Agreement for worsening (inter-reader, and BLOKS-vs-WORMS), and frequencies of worsening are shown below:

	BLOKS Worsening	WORMS Worsening	
	by either extent or depth	whole grade	Whole or within-grade
inter-reader agreement	k=0.88	K=0.65	k=1.00
% knees worsening	29%	27%	38%
agreement with BLOKS (either extent or depth)	--- ---	88% agreement K=0.71	82% agreement k=0.61

The following table shows that varus alignment (<=2º) and high body mass index (BMI) increased the risk of worsening medial compartment cartilage scores [odds ratios (OR) adjusted for age, sex, BMI]:

Adjusted OR [95% CI] for predictor	Outcome: BLOKS Worsens	Outcome: WORMS Worsens	
	by either extent or depth	Whole grade	whole or within-grade
Varus (vs non-Varus)	6.50 [1.49-28.26]	2.34 [0.71-7.70]	1.88 [0.68-5.19]
BMI (per SD increase)	2.39 [1.19-4.82]	1.77 [0.98-3.20]	1.24 [0.76-2.04]

CONCLUSIONS: WORMS and BLOKS both had good to excellent inter-rater reliability, with good agreement between them on the presence of whole grade worsening within a knee. Using "within-grade" worsening in WORMS increased sensitivity for progression, but at a tradeoff with less association with risk factors for OA progression. The validity of the additional "within-grade" change score requires further investigation. The large amount of change required for a transition from BLOKS grade 2(10-75% of a region) to grade 3 (>75% of a region) may limit sensitivity for scoring change while increasing specificity and association with risk factors.

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Osteoarthritis Imaging:

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