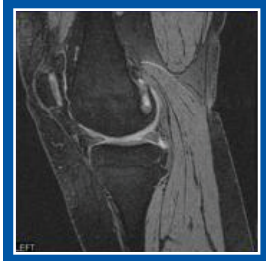

Why Aren't We There yet?

Re-examining Standard Paradigms in Imaging of OA

2nd Annual Workshop on

Imaging Based Measures of Osteoarthritis

June 25th - 28th 2008
Boston, MA USA

Richard E. Wylie Conference Center, Beverly, MA

New England Baptist Hospital

Beth Israel Deaconess Medical Center

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2nd ANNUAL WORKSHOP ON IMAGING BASED MEASURES OF OSTEOARTHRITIS

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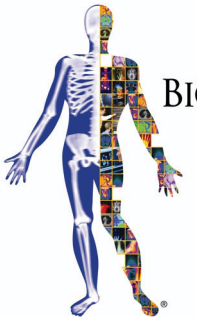

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Why Aren't We There yet?

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http://nebh.org/display.asp?node_id=10649

In the late 1980s, the application of the superb soft tissue contrast of MRI to image the joint led to great optimism that inroads to understanding the natural history of, and applying therapeutics to, osteoarthritis would be quickly forthcoming. However, nearly 20 years later, much about clinical OA has yet to be discovered, there is yet to be a successful trial for a disease modifying OA drug (DMOAD), and radiography is still the mainstay of imaging of OA.

The goal of the current workshop is to bring together the communities of basic osteoarthritis researchers, orthopedists and rheumatologists, imaging scientists, instrument manufacturers, and pharmaceutical and regulatory representatives to delineate what the pressing questions are in OA research, what imaging science has contributed thus far, what questions imaging can start to address, and what resources are needed to accomplish this.

Organizers:

Deborah Burstein, Beth Israel Deaconess Medical Center, Boston, MA USA.
dburstei@bidmc.harvard.edu

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Dr. Ali Guermazi Boston University Medical Center, Boston, MA
Dr. Young Jo Kim Childrens Hospital, Boston, MA
Dr. Grace Lo Tufts University/NEMC, Boston, MA.
Dr. Linda Sandell Washington University School of Medicine, Saint Louis, MO
Dr. Marie-Pierre Hellio Le Graverand-Gastineau Pfizer, Groton, CT
Dr. Charles Mamisch University Berne, Switzerland

Why Aren't We There yet?

Re-examining Standard Paradigms in Imaging of OA

2nd Annual Workshop on Imaging Based Measures of Osteoarthritis

Program

Why Aren't We There yet?

Re-examining Standard Paradigms in Imaging of OA

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Wednesday, June 25:

07:30 - 09:00 **Breakfast and Registration**

09:00 - 09:15 **Welcome: David Hunter and Deb Burstein**

09:15 – 09:30 **Setting the stage: 3 case studies:** **David Hunter** and **Deb Burstein**
Case A: Mr. A. Symptomatic : 50 y.o. without prior joint complaints
Case B: Ms. A.C.L. Tear : 25 y.o. with recent traumatic tear of ACL
Case C: Mr. I.M. Pained : 65 y.o. with 10 year history of painful right knee

Paradigm of 2008 Universe: Current diagnostics / treatment plan
Paradigm of 2028 Universe: Where do we want to be for diagnostics / treatment?

Review of current definition of OA: "Osteoarthritis (OA), which is also known as osteoarthrosis or degenerative joint disease (DJD), is a progressive disorder of the joints caused by gradual loss of cartilage and resulting in the development of bony spurs and cysts at the margins of the joints."

09:30 – 10:00 **Joint biology** **Linda Sandell**
Normal growth and breakdown; different tissue targets, ie cartilage, bone, meniscus; unknowns in biology

10:00 – 10:30 **OA Pathophysiology** **Stefan Lohmander**
What tissues are affected, natural temporal and spatial evolution of tissue changes, how and in what order are they affected, what mediates these structural changes (molecular and macroscopic factors)

10:30 – 10:45 **Break**

10:45 – 11:15 **Biomechanics** **David Wilson**

Mechanics (Normal, abnormal, effect on biology / pain / potential for biological and/or biomechanical therapeutics in light of biomechanics)

11:15 – 11:45 **Pain** **Laurence Bradley**
Biological source, clinical assessment, therapeutics of source / perception)

11:45 – 12:15 **Clinical Trials** **Marie-Pierre Hellio Le Graverand-Gastineau**
What are the current models of clinical trials for understanding and evaluating therapeutics in OA - What outcome metrics are used.

12:15 – 12:45 **Questions / Discussion**

12:45 – 14:00 **Lunch**

14:00 – 14:30 **Current imaging techniques in OA diagnostics** **Philip Conaghan**
Overview of current imaging as applied to OA diagnostics; What methods are we currently using, and what are the limitations?

14:30 – 15:15 **MRI of the joint; where we started, where we are, and why arent we there yet?** **Deb Burstein**

15:15 – 16:00 **Questions / Discussion**

16:00 – 16:15 **Break / Refreshments**

16:15 – 17:00 **Redefining OA:** **Stefan Lohmander**
Discussion of proposal for definition of OA (for use / revision during the remainder of the meeting)

17:00 – 18:30 **Posters / refreshments**

19:00 **Dinner at Peabody Essex Museum**

08:00 – 09:00 **Breakfast**

09:00 – 10:30 **What can we learn from modalities other then MRI / other clinical trials / other areas of drug development that were successful or not; why were they successful / why did they fail?**

09:00 – 09:30 **Other imaging modalities for use in OA:** CT, PET, Ultrasound **Ali Guermazi**
09:30 – 10:00 **Osteoporosis** **Harry Genant**
10:00 – 10:30 **Rheumatoid arthritis** **Philip Conaghan**

10:30 – 11:00 **Questions / Discussion**

11:00 – 11:15 **Break / refreshments**

11:15 – 11:35 **The regulatory setting** **Sarah Okada**
What is currently the accepted regulatory and future vision for imaging, and the rate limiting steps in attaining the future vision

11:35 – 11:55 **The pharmaceutical industrial setting** **Jeff Evelhoch**
Rationale for current focus, does this focus need to change, and rate limiting steps in changing this position

11:55 – 12:15 **The imaging industrial setting** **Charles Mamisch**
Are the technologies / implementations being constrained such that their maximum utility is not being achieved?

12:15 – 12:30 **Conference Photo**

12:30 – 14:00 **Lunch Discussion: Young Jo Kim**
What should the ideal imaging package for OA consist of?
(Supported by Siemens)

14:00 – 15:30 **Breakout sessions**

15:30 – 15:45 **Break / refreshments**

15:45 – 17:30 **Discussion on recommendations from breakout sessions**

17:30 –19:00 **Posters / refreshments**

19:00 **Dinner at Tupper Manor**

Friday, June 27

08:00 – 09:00 **Breakfast**

09:00 – 12:00 **WORKSHOP: Revisiting main questions from the meeting to compile a "white paper" of recommendations**

12:00 – 13:00 **Review of recommendations**

13:00 – 14:00 **Lunch (Supported by Merck)**

15:00 – 17:00 **Afternoon of social activities: Duck Tour of Boston**

19:30 **Dinner at Omni Parker Hotel**

Saturday, June 28

Post congress family-friendly tour:

09:00 -13:00 **Whale Watching in Gloucester**

13:00 – 14:00 **Lunch at Woodman's of Essex**

15:00 – onwards **Free time: Antique tour in Essex/ Canoeing**

Why Aren't We There yet?

Re-examining Standard Paradigms in Imaging of OA

2nd Annual Workshop on Imaging Based Measures of Osteoarthritis

Abstracts

Poster Presentations

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1	Attendees	Redefining OA
2	Attendees	What Have We Learned About Joint Health And Disease Through The Use Of MRI?
3	Attendees	What We Need To Know About Joint Health And Disease
4	Attendees	Resources Needed For Imaging OA
5	Ananda, Ana	Effects of Weight Loss on Articular Cartilage Proteoglycan Content: A Pilot Study Utilizing dGEMRIC at 3T
6	Aspden, Richard	Is Generalized Osteoarthritis A Problem Of Growth Not Decay?
7	Bae, Kyongtae Ty	Knee Cartilage-Joint Tissue Contrast Improves When Dess-We MR Images Are Reconstructed As The Geometric Mean Instead of Arithmetic Mean Of Double Echo Images
8	Benichou, Olivier	One Year Change In Radiographic Joint Space Width In Patients With Baseline Unilateral Joint Space Narrowing- Data From The Osteoarthritis Initiative (OAI)
9	Bowers, Megan	Quantifying Meniscal Volume and Tibiofemoral Cartilage Thickness After Partial Meniscectomy
10	Buck, Robert	Location and Magnitude of Cartilage Thickness Loss In OA Progressor
11	Chen, Christina	Three-Dimensional Isotropic MRI Methods for Rapid Assessment of Cartilage Morphology in the Knee
12	Duryea, Jeffrey	Effect of Sub Optimal Subject Positioning and X-Ray Beam Alignment on the Measurement of Radiographic Joint Space Width: Analysis of Longitudinal Data from the Osteoarthritis Initiative (OAI)
13	Duryea, Jeffrey	Study of Location Specific Lateral Compartment and Radiographic Joint Space Width for Knee Osteoarthritis Progression: Analysis of Longitudinal Data from the Osteoarthritis Initiative (OAI)
14	Eckstein, Felix	Knees with X-Ray Joint Space Narrowing Have Greater MR-Based Cartilage Loss-Data From The Osteoarthritis Initiative (OAI)
15	Elliot, Margaret	The Canadian Arthritis Network's Unique Model of Consumer Involvement in Research
16	Elliot, Margaret	Consumers: Equal Partners in Research
17	Frobell, Richard	The Acutely ACL Injured Knee Assessed By MRI: Morphometric Change of Cartilage Over The First Two Years After Injury
18	Gold, Garry	Repeatability of IN VIVO Sodium MRI of Cartilage In Early OA
19	Hellio Le Graverand, Marie Pierre	Two Year Longitudinal Changes In Regional Cartilage Morphology In a Multicenter, Multivendor MRI Study At 3.0T The A9001140 Study
20	Huang, Feng	Toward Automatic Articular Cartilage Segmentation From MRI: Distance Constrained Segmentation
21	Hunter, David	Cartilage morphometry region of interest analysis; by selecting regions with denuded areas can we detect greater amounts of change?
22	Hunter, David	Relation of regional articular cartilage morphometry and meniscal position by MRI to joint space width in knee radiographs.

Poster Presentations (cont'd)

Poster #	First Author	Title of Abstract
23	Jacobson, J.J.	Accelerated Parametric Imaging Using Image Estimation Methods
24	Johnston, James	Quantitative Computed Tomography (QCT) Should Replace Dual-Energy Absorptiometry (DXA) When Assessing The Osteoarthritic Knee
25	Johnston, James	In-VIVO and In-VITRO Precision of Computed Tomography Topographic Mapping of Subchondral Density (CT-TomasD) In The Proximal Tibia
26	Koo, Seungbum	Toward Automatic Segmentation of Knee Articular Cartilage In Osteoarthritis initiative MRI Data Using Machine Learning
27	Krasnokutsky, Svetlana	Synovial Volume and Bone Marrow Edema on MRI Predict Radiographic Severity of Knee Osteoarthritis and Correlate with TNFa Expression in Peripheral Blood Leukocytes
28	Kress, I.	MRI Based Morphologic Grading System For Early Hip Osteoarthritis
29	Lacey, T.	Comparison Of X-Ray and MRI In The Determination of OA Progression In The Knee Measured At A Fixed Load-Bearing Position In The Medial Compartment
30	Lalone, Emily Allen	Development of An Image-Based Technique To Quantify Contact Area in the Ulnohumeral Joint
31	Losina, Elena	The Public Health Implications Of Defining Early Osteoarthritis: The Tip Of The Iceberb
32	Maschek, Susanne	Quantitative MR Imaging of Cartilage Morphology in the Presence of Gd-DTPA is Less Sensitive to Longitudinal Change in OA
33	McWalter, Emily	Effect Of A Patellar Brace On Three-Dimensional Patellar Tracking In Subjects With Knee Osteoarthritis
34	Multanen, J.	Reproducibility of dGEMRIC in the Human Knee Joint at 1.5 T
35	Neogi, Tuhina	Radiographic Features of Osteoarthritis Are Strongly Associated with Knee Pain: The Issue is Settled
36	Piscaer, Tom	Folate mediated imaging of activated macrophages in experimental osteoarthritis using SPECT/CT
37	Portnoy, Roman	Delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) After ACL Tear
38	Roemer, Frank	Semiquantitative Assessment Of Peripatellar Synovitis In Osteoarthritis: A Comparative Study Of Non-Enhanced VS. Contrast-Enhanced MRI
39	Roemer, Frank	Contrast-Enhanced MRI Of Subchondral Cysts: The Most Study
40	Samuels, Jonathan	Can Musculoskeletal Ultrasound Contribute Significantly to OA Research
41	Schneider, Ericka	OAI MR Quality Assurance Methods and Results
42	Shim, Hackjoon	Segmentation of Knee Cartilages On 3.0T MR Images From The Osteoarthritis Initiative (OAI) With a Semi-Automated Graph-Cuts Method and A Manual Delineation Methods

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Poster #	First Author	Title of Abstract
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44	Tamez-Pena, Jose	3D Method For The Automated Analysis Of The Knee Joint Space: MRI Data From The Osteoarthritis Initiative
45	Thedens, Dan	Age, DJD, OA: AGE, GAG, T1p MRI
46	Totterman, Saara	Bone/Cartilage Interface Events In OA - Do They Matter
47	Totterman, Saara	From Healthy To Osteoarthritic Knee Joint; The Road To Be Traveled
48	Trattnig, Siegfried	Delayed Gadolinium MRI of Cartilage (dGEMRIC) For Assessment Of Cartilage Maturation After Repair Surgery: Clinical Protocol Using Fast Sequence Technique, Value of Non-Contrast and Comparison Of Different Therapies
49	Wang, L.	Rapid Isotropic 3D-Sodium MRI of Knee Joint In-vivo at 7T
50	Wang, Manyi	Quantitative MRI Study of Cartilage Tribology
51	Williams, T.G.	Statistical Shape Modelling Reveals Focal Pattern of Cartilage Loss In OAI Progression Cohort Type of Abstract
52	Wirth, Wolfgang	Spatial Patterns of Catilage Loss In The Medial Femoral Condyle-Data From The Osteoarthritis Initiative
53	Wyman, Bradley	Comparison Of One Year change In Minimum Joint Space Width To Fixed Location Joint Space Width To Fixed Location Joint Space Measurements In Lyon Schuss X-Rays From The A9001140 Study
54	Xia, Yang	Reorganization Of The Extracellular Matrices In Compressed Cartilage By Polarized Light Microscopy and Fourier-Transform Infrared Imaging
55	Xia, Yang	Multidisciplinary View Of The Depth-Dependent Properties Of Articular Cartilage
56	Xia, Yang	Imaging-Based Measures Of Early Osteoarthritis Are Possible, If You Have Microscopic Resolutions
57	Xie, Liqin	Assessment of Cartilage Morphology and Composition in a Rat Joint Degradation Model via EPIC-uCT
58	Yoo, Ji Hyun	Automatic Bone Registration For Cartilage Morphological Analysis On Knee MR Images From Osteoarthritis Initiative (OAI)
59	Zhou, Zhi-yang	Regional Changes Of T1p Relaxation On Porcine Patellar Cartilages In Vitro By Means Of Degradation Enzymatically

REDEFINING OA

“Osteoarthritis (OA), which is also known as osteoarthrosis or degenerative joint disease (DJD), is a progressive disorder of the joints caused by gradual loss of cartilage and resulting in the development of bony spurs and cysts at the margins of the joints.”

This definition leaves out a number of factors which are now known to be important in the disease process. In addition, there is more focus on better understanding of joint health, in order to better understand disease. While this group is not in a position to redefine OA in a general sense, it may be beneficial to redefine what should be the focus of our investigations into joint health and disease for the purposed of the discussions to follow. Table to be filled out during the Workshop.

PROPOSED NAMES

WHAT HAVE WE LEARNED ABOUT JOINT HEALTH AND DISEASE THROUGH THE USE OF MRI?

MRI of the soft tissues of the knee was first described in 1984 (Li KC, Henkelman RM, Poon PY, Rubenstein J. MR imaging of the normal knee. J Comput Assist Tomogr 1984;8(6):1147-1154.). Various techniques for investigating the macromolecular content / structure of cartilage, including T2, diffusion, magnetization transfer, dGEMRIC, and T1rho, were first demonstrated 10 to 20 years ago.

Despite the availability of MRI for over a decade, few bench or clinical trials are utilizing MRI techniques as probes into disease detection or mechanisms, and methods for maintaining joint health and treating disease still remain largely unknown.

At this juncture it is critical to begin to assess specifically what information has been gleaned from MRI in order to focus on what has been achieved, thus enabling a better evaluation of whether past directions have been effective or need to be changed. The table below is meant as a beginning of this process; the table will be filled in during the workshop.

WHAT WE'VE LEARNED	REFERENCE / Technique used	IMPLICATIONS FOR JOINT HEALTH / DISEASE

WHAT WE NEED TO KNOW ABOUT JOINT HEALTH AND DISEASE

Many techniques are currently available for imaging the joint. The basic procedures are available for bench and clinical application. It is imperative to tailor the imaging protocols to questions of interest to biology / biomechanics / clinical medicine. The table below is meant as a beginning of this process; the table will be filled in during the workshop.

WHAT WE NEED TO KNOW	SUGGESTED STUDY DESIGN

RESOURCES NEEDED FOR IMAGING OA
(TO BE FILLED OUT DURING WORKSHOP)

RESOURCES NEEDED	IMPACT

EFFECTS OF WEIGHT LOSS ON ARTICULAR CARTILAGE PROTEOGYLCAN CONTENT: A PILOT STUDY UTILIZING dGEMRIC AT 3T

[*]Anandacoomarasamy A., [**]Caterson I., [*]Smith G., [*]Leibman S., [*]Giuffre B., [***]Fransen M., [*]Sambrook P., [*]March L.

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[***]George Institute, Sydney, Australia

Introduction: Delayed gadolinium enhanced magnetic resonance imaging of cartilage (dGEMRIC) of the knee is used to assess the relative distribution of glycosaminoglycan in cartilage. Few studies have utilized a 3T MRI scanner.

OBJECTIVE: To assess dGEMRIC in obese subjects undergoing weight loss over 12 months.

METHODS: 37 obese subjects (BMI >30) recruited from weight loss programs 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 in the mid-coronal, medial sagittal and lateral sagittal planes were obtained 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. T1Gd maps were generated with pixel-by-pixel 3-parameter T1 fit using Matlab software (The MathWorks, Natick, MA). In the sagittal plane, this was the weight-bearing femoral cartilage and all the tibial cartilage. In the coronal image, this was all cartilage in view. The dGEMRIC index was calculated for 8 regions of interest and averaged for whole coronal, medial and lateral compartments, both uncorrected and corrected for BMI dose bias. The change in BMI and dGEMRIC index for each compartment was calculated. Regression analysis was used to assess the relationship between change in BMI and change in dGEMRIC index.

RESULTS: There were 24 women and 13 men. Mean BMI at follow up was 37.2 ± 6.1 (range 21.4 – 49.6). The mean absolute and percentage change in BMI was -3 (± 3.7) and -7.4 (± 9.1) respectively. The average uncorrected dGEMRIC index at 12 months for whole coronal, medial sagittal and lateral sagittal compartments was 502 ± 71 msec, 532 ± 66 msec and 539 ± 55 msec respectively. Mean change in uncorrected dGEMRIC index at 12 months in the 3 compartments was -29 (± 70), -15 (± 99), and -10 (± 64) respectively. There was statistically significant association between percentage change in BMI and lateral sagittal compartment dGEMRIC index ($p<0.05$), noted with and without correction for BMI. Those who lost more weight had lower mean loss (or gain) in dGEMRIC index in all 3 compartments but this did not reach statistical significance. Intra-rater reliability revealed ICCs >0.91.

CONCLUSION: This pilot study demonstrates a significant association between the change in lateral sagittal dGEMRIC index and change in BMI, indicating lower decline in dGEMRIC index with weight loss. This is promising as it indicates weight loss may influence articular cartilage proteoglycan content. However, a wide range of dGEMRIC indices was observed and further study with a larger sample size is necessary. The natural rate of change also needs to be assessed in order to determine clinically important differences.

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DISCLOSURE STATEMENT: none
ACKNOWLEDGEMENT: Professor Deborah Burstein for expert advice
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IS GENERALIZED OSTEOARTHRITIS A PROBLEM OF GROWTH NOT DECAY?

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Which tissue comes first? And what drives joint degeneration? These questions are among the most pressing in understanding generalised primary OA and getting answers to these could lead to new biomarkers and novel therapeutic targets. But is cartilage OR bone OR muscle the right question? If we recognise that OA affects cartilage AND bone AND muscle etc., and that they all derive developmentally from a mesenchymal origin does this indicate that there may be a common underlying driver of all these changes?

I hypothesize that generalized OA is a systemic disease of the musculoskeletal system characterised by dysregulated growth of tissues arising form a reversion to an earlier developmental cell phenotype. This results in new tissue being formed in the wrong place and at the wrong time leading to loss of proper mechanical function. In bone this is shown by subchondral bone sclerosis, the change in shape of the affected joints and formation of marginal osteophytes by a reversion to endochondral ossification, changes concomitant with or preceding cartilage changes. There is hypertrophy and fibrosis of ligaments and the joint capsule and an increase in adiposity, both subcutaneous and central, with increased fat in the bone marrow. The link with obesity may be metabolic, via adipokines, and not solely biomechanical. Even changes in cartilage, traditionally seen as degenerative, appear to have their origins in proliferation of chondrocytes, increased synthesis of matrix molecules, though not their incorporation into tissue, a re-expression of collagen type IIA, normally seen during development, and multiplication of the tidemark. Alongside these connective tissue changes are weakness and a change in fibre type in muscles, and central and peripheral nervous sensitization leading to the deep, intractable pain experienced by sufferers.

If the disease is centrally driven what could be the underlying causes? Genetic linkages and haplotype associations are being uncovered but these are relatively weak and no consistent pattern has yet been identified. Epigenetic changes however, such as chromatin modifications, have also been found to be hereditary between generations and maybe the search needs to be widened in this direction. Short-stranded micro-RNAs can act as mediators of RNA interference and lead to silencing of their target genes. Some of these have been found to regulate cell division and apoptosis, metabolism and tumour proliferation and there is some evidence for nutrition-related activation of these mechanisms. The central regulation of bone (and metabolism) via the hypothalamus and the discovery of a multitude of neuropeptides and related enzymes in bone and other connective tissues raises the question of whether the central nervous system may play a pivotal role in the dysregulation outlined above. Could OA start in the brain?!

Investigating OA in a broader context may provide new biomarkers, imaging and metabolic, and could lead to earlier recognition of disease, earlier intervention and new drug targets.

DICLOSURE STATEMENT: RMA is in receipt of funding from TMRI Ltd.
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KNEE CARTILAGE-JOINT TISSUE CONTRAST IMPROVES WHEN DESS-WE MR IMAGES ARE RECONSTRUCTED AS THE GEOMETRIC MEAN INSTEAD OF ARITHMETIC MEAN OF DOUBLE ECHO IMAGES

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INTRODUCTION: Accurate segmentation and quantification of knee cartilage from MR images requires a high MR signal contrast between the cartilage and joint tissues, even more so than the MR signal contrast between the cartilage and bone. In the present implementation of Double Echo Steady State with Water Excitation (DESSwe) knee MR imaging such as in Osteoarthritis Initiative (OAI), each DESSwe image is reconstructed as the arithmetic mean of the first and second (double) echo images. In theory, the geometric mean reconstruction of DESSwe MR imaging is superior to the arithmetic mean reconstruction for the enhancement of cartilage-joint tissue contrast.

OBJECTIVE: To compare the image quality, specifically knee cartilage-joint tissue contrast, between the geometric- and arithmetic-mean reconstructions of DESSwe images.

METHODS: The raw MR data acquired from recent DESSwe MR imaging of six knee studies were saved offline. From each raw dataset, the first and second echo images were individually reconstructed using Fast-Fourier-Transfer (FFT). Two sets of DESSwe images were reconstructed from the double-echo images at each slice position: one set corresponding to the geometric-mean (GM) and the other set corresponding to the arithmetic-mean (AM) of the double-echo images. Signal intensities were measured over various regions (bone, cartilage, meniscus, joint fluid, and background air) on mid-sagittal GM and AM images. Signal-to-Noise (SNR) values of the bone, cartilage, meniscus, and joint fluid were calculated. From these, Contrast-to-Noise (CNR) values of the cartilage to the adjacent structures (bone, meniscus, and joint fluid) were computed. Differences in SNR and CNR values between the GM and AM images were evaluated using paired t-test. In addition, qualitative assessment of the image quality and cartilage tissue contrast was performed.

RESULTS: SNR of the GM images was consistently lower than that for the AM images in all tissue measurements (GM versus AM): (1.4 versus 1.7) for bone, (13.3 versus 14.9) for cartilage, (5.8 versus 8.1) for meniscus, (23.3 versus 23.7) for joint fluid ($p<0.01$). The cartilage-bone CNR was also slightly lower on the GM than AM images (group mean ± SD: 11.9 ± 2.7 versus 13.3 ± 2.9, $p<0.01$). However, the CNR of the cartilage-to-joint was higher for the GM than AM images: (7.5 ± 2.3 versus 6.8 ± 2.0, $p<0.01$) for cartilage-meniscus and (9.9 ± 3.8 versus 8.7 ± 3.7, $p<0.01$) for cartilage-joint fluid. Qualitative assessment correlated well with quantitative results.

CONCLUSION: Compared to the arithmetic-mean reconstruction, the geometric-mean reconstruction of DESSwe MR images yielded higher cartilage-joint tissue contrast but lower cartilage-bone contrast. Although this is a trade-off, the geometric-mean reconstruction is likely advantageous over the arithmetic-mean reconstruction since the cartilage-joint tissue interface is more difficult to delineate than the cartilage-bone interface for the segmentation of cartilage.

SPONSOR: Osteoarthritis Foundation Western Pennsylvania Chapter.
DICLOSURE STATEMENT: Kwoh C.K. has grants funded by Astra-Zeneca and Beverage Institute
ACKNOWLEDGMENT: OAI
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ONE YEAR CHANGE IN RADIOGRAPHIC JOINT SPACE WIDTH IN PATIENTS WITH BASELINE UNILATERAL JOINT SPACE NARROWING - DATA FROM THE OSTEOARTHRITIS INITIATIVE (OAI).

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INTRODUCTION: Identification of subjects with a high risk of progression of structural changes is necessary for clinical trials in knee OA. Prior studies have suggested that participants with asymmetric knee OA severity may allow to assess disease progression in both early and more advanced disease.

OBJECTIVE: We examined the rate of loss of joint space width (JSW) in both knees from patients with unilateral joint space narrowing (JSN) at baseline.

METHODS: Data for these analyses are from the OAI public use data sets (1.2.1 Clinical Data set and 1.B.1 Imaging Data set), a multi-center, longitudinal cohort study designed to identify biomarkers for the development and progression of symptomatic knee OA. Patients were selected based on: bilateral frequent pain, BMI>25, unilateral medial JSN (OARSI grade 1-3). The patients were selected based on radiographs read at each site and then re-read centrally to confirm unilateral medial JSN.
Baseline and year 1 fixed flexion radiographs of both knees were read (blinded to time point) for medial joint space width (JSW) at the location of the minimal distance between the femur and tibia margins (mJSW) and at 4 locations (x = 0.2, 0.225, 0.25, and 0.275), in a previously described coordinate system. Seventy participants met the criteria: 46 women / 24 men, age = 60 ± 9 y, BMI = 31 ± 4, bilateral chronic frequent knee pain. Knees with baseline medial JSN (JSN knees) had OARSI JSN grades of 1, 2, or 3, in respectively 42, 21, and 7 while all no-JSN knees had an OARSI grade 0 JSN at baseline. A definite osteophyte was observed in a least one knee of 40 patients (in 37 JSN knees and 16 no-JSN knees).

RESULTS: The average progression in no-JSN knees was similar to that in JSN knees (table). However the variability in progression was higher in the no-JSN knees than in the JSN knees, which is reflected in the no-JSN knees' higher SRMs. In this population, baseline JSW in any knee did not predict radiographic progression in the ipsilateral or contralateral knee (whatever the location).

Table: One year change in joint space width (mm). *SRM = mean/SD. FDR p = false discovery rate.*

	JSN knees (n = 70)				No-JSN knees (n=70)			
Variable	Mean	Std	SRM	FDR p	Mean	Std	SRM	FDR p
X = 0.2	-0.16	0.44	-0.38	0.005	-0.22	0.83	-0.26	0.05
X = 0.225	-0.20	0.48	-0.41	0.005	-0.19	0.80	-0.24	0.05
X = 0.25	-0.19	0.53	-0.37	0.005	-0.20	0.76	-0.26	0.05
X = 0.275	-0.18	0.54	-0.34	0.007	-0.23	0.74	-0.31	0.05
mJSW	-0.11	0.41	-0.28	0.02	-0.19	0.78	-0.25	0.05

CONCLUSION: Patients selected from the OAI database based on unilateral medial JSN (as well as BMI>25 and bilateral knee pain), had an average annual change in JSW very similar in JSN knees versus no-JSN knees. However, the higher variability of change in the no-JSN knees resulted in lower sensitivity to change in these knees as compared to the JSN-knees. The x-coordinate system appeared more responsive than mJSW in JSN-knees.

SPONSOR: Eli Lilly & Co, Indianapolis, IN.
DISCLOSURES: O.D.Benichou & D.R.Nelson are employees of Eli Lilly. F.Eckstein is CEO of Chondrometrics GmbH & provides consulting services to Pfizer, MerckSerono, & Wyeth. K.Kwoh received grants from the Beverage Institute, Astra-Zeneca, and has equity interest & serves on the Cartesia Dx Scientific Board.
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QUANTIFYING MENISCAL VOLUME AND TIBIOFEMORAL CARTILAGE THICKNESS AFTER PARTIAL MENISCECTOMY

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INTRODUCTION: Partial meniscectomy is routinely performed to alleviate symptomatic tears. However, it is unknown whether there is a critical amount of meniscal tissue that can be removed without diminishing its chondroprotective function. The use of qMRI to measure meniscal volume and articular cartilage thickness has recently been validated *ex vivo* (Bowers 2007; 2008), but must be validated *in vivo*.

OBJECTIVE: To assess the reliability of these methods before and after surgery in patients undergoing partial meniscectomy. This pilot study was designed to validate tools for the future long-term evaluation of partial mensicectomy patients. We expected a decrease in the volume of the resected menisci after surgery, but not in the uninjured menisci, or in cartilage thickness, over the 1-month study interval.

METHODS: The injured knees of 9 subjects were imaged at 3T (Siemens Trio, Erlangen, Germany) prior to and 1 month following unicompartmental partial meniscectomy. The T2*-3D-CISS (0.3x0.3x1.0mm) and the T1-WE-3D FLASH (0.3x0.3x1.5mm) sequences were used to image the menisci (Bowers 2007) and cartilage (Eckstein 2004; Bowers 2008), respectively. The tibiofemoral cartilage of each knee was manually segmented in the sagittal plane and reconstructed using commercial software (Mimics 9.11); the menisci were manually segmented in the sagittal and coronal planes. 3D voxel models were generated and wrapped with a triangular mesh to create a solid model of each structure. The volume of each meniscal model was calculated by surface integration. Cartilage thickness measurements were performed on load-bearing regions of interest (ROIs). A cylinder was fit to the bone-cartilage interface of the femoral cartilage model. A line was drawn from a notch on the lateral condyle to the cylinder's center. Each femoral condyle was divided from the notch point toward the posterior aspect of the femur to create 6 femoral ROIs. Two tibial ROIs were also defined. The inertial axes of the medial compartment and the centroid of each compartment were calculated with MATLAB. The calculated inertial axes were projected onto the centroid of each tibial compartment to determine ROI orientation. The mean thickness of each cartilage patch was calculated with a closest point algorithm using MATLAB (Bowers 2008). Two-way repeated measures ANOVAs were performed to compare meniscal volume in response to surgical time point (pre- vs post-operative) and meniscus (injured vs uninjured). One-way repeated measures ANOVAs were performed in each cartilage ROI to compare pre- and post-operative cartilage thickness values.

RESULTS: The mean pre-operative volume of the injured menisci was significantly greater than the post-operative volume ($p<0.001$), and there was no significant difference between the mean pre-operative and post-operative volumes of the uninjured menisci ($p=0.88$; Fig 1). There was no significant difference between the mean pre-operative and post-operative thickness of any cartilage ROI ($p>0.13$).

CONCLUSION: Our data demonstrate that the described segmentation techniques are able to quantify meniscal volume and cartilage thickness *in vivo* in patients treated with partial meniscectomy. As expected, significant differences were seen between pre- and post-operative volumes of the resected menisci ($p<0.001$); and no significant differences were observed in the uninjured menisci, or in any cartilage ROI, after surgery. This approach may offer a novel method to study the relationship between the volume of meniscal tissue removed and subsequent changes in articular cartilage thickness.

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DISCLOSURE STATEMENT: Nothing to disclose.
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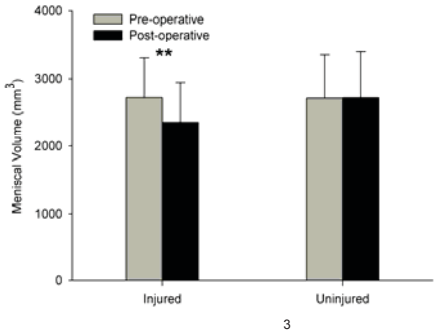

Figure 1: Mean volumes (mm^3) of the injured and uninjured menisci, before and after partial meniscectomy. **denotes $p<0.001$. Error bars indicate standard deviations.

LOCATION AND MAGNITUDE OF CARTILAGE THICKNESS LOSS IN OA PROGRESSORS

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INTRODUCTION: A 2 year study to compare change in cartilage thickness in non OA and OA subjects, also provides an opportunity to identify individuals with significant decrease in cartilage thickness, i.e., progressors. Examination of only progressors may lead to better understanding of the location and magnitude of changes in cartilage thickness over a period of time typically used in clinical trials.

OBJECTIVE: To identify subjects with significant medial cartilage thickness decrease over two years and assess the location and magnitude of their decrease.

METHODS: In the A9001140 study, 152 female subjects were imaged at 7 clinical centers using Siemens Magnetom Trio and GE Signa Excite magnets. Double oblique coronal acquisitions were obtained at baseline and 2 years, using water excitation spoiled gradient echo sequences (1.0 x 0.31 x 0.31mm^3 resolution). Segmentation of femoro-tibial cartilage morphology was performed using proprietary software (Chondrometrics GmbH, Germany). Change in medial cartilage thickness (ThCtAB.aMe) over 24 months was measured for the whole compartment (cMFTC, MFTC), the femoral and tibial plates (cMF, MT), 3 subregions of the femoral plate (ccMF, ecMF, icMF) and 5 subregions (central, exterior, interior, anterior and posterior) of the tibial plate (cMT, eMT, iMT, aMT, pMT). Kellgren and Lawrence grades (KL) were observed on standing anteroposterior (AP) and Lyon Schuss (LS) radiographs of the knee.

The 77 subjects with KL=0 scores on both AP and LS radiographs were viewed as an unambiguous healthy group and defined as non OA subjects. Of the remaining 75 subjects, 13 had KL=0 only on the AP radiographs, 4 were KL=1, 30 were KL=2, and 28 were KL=3. While some subjects had AP KL=0, for convenience this group was defined as the OA group. Progressors were defined as subjects with a larger decrease in a cartilage thickness measure than expected from examination of non OA distribution. Normalized values (z-scores) were generated for non OA and OA subjects by subtracting the mean and standard deviation of the non OA subjects. Specifically, the normalized values were translated to *p* values from the normal distribution and small *p* values were taken as indication of progression. Multiple comparisons adjustments were made using false discovery rate methods (α = 0.1) for non OA and OA groups separately. Normality plots were used to check if annualized rates of change in cartilage thickness for the non OA group were normally distributed. Summary statistics regarding frequency and magnitude of progression in different KL Groups and knee regions were computed.

RESULTS: 28% of the OA group were progressors, compared to 2.6% of the non OA group. Using AP radiograph KL scores, 20% of KL2s were progressors compared to 46% of KL3s. Twelve of the 23 progressors had significant progression in a single subregion, while 4 had significant progression in 4 or more subregions. Approximately 10% of subjects had significant progression when observing compartments (cMFTC, MFTC), while 5 – 8% had progression when observing medial plates (cMF, MT). The subregion with highest observed frequency of progression was eMT (65% of progressors) followed by ccMF (35%). Mean percent annualized rate of change in progressors ranged from -0.6% (pMT) to -5.9% (eMT) with 4 of the subregions having annual percent decrease in thickness greater than 3%. Rate of change in non progressors ranged between -0.3 to 0.7%.

CONCLUSION: Over 2 years many subjects do have a significant decrease in cartilage thickness, but the decrease tends to be localized (1 subregion). Although two subregions, eMT and ccMF, are the most frequently observed locations for decrease in cartilage thickness, all subregions, except perhaps pMT, are observed to have important decreases in some subjects.

SPONSOR: Pfizer Inc.
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THREE-DIMENSIONAL ISOTROPIC MRI METHODS FOR RAPID ASSESSMENT OF CARTILAGE MORPHOLOGY IN THE KNEE

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INTRODUCTION: Clinical imaging protocols and longitudinal studies of osteoarthritis (OA) often use a combination of two-dimensional fast spin-echo (2D-FSE) for internal derangements of the knee and high-resolution 3D spoiled gradient echo (3D-SPGR) for articular cartilage. This approach is limited by anisotropic voxels and blurring on 2D-FSE, and dark synovial fluid on 3D-SPGR. A single sequence that could provide accurate cartilage volumes and diagnose internal derangements would be useful.

OBJECTIVE: This study tests whether two alternative MR imaging techniques can each replicate the advantages of a combined 2D-FSE/3D-SPGR protocol in a single acquisition. The two techniques 1) 3D-FSE acquisition using an extended echo train acquisition and 2D-accelerated auto-calibrated parallel imaging (3D-FSE-Cube) and 2) VIPR are compared to SPGR with water/fat separation (IDEAL-SPGR) and parallel imaging. Recent work has found these methods to successfully evaluate internal derangements of the knee. This study investigates the potential of these methods in cartilage evaluation, specifically knee cartilage volumes.

METHODS: Ten knees of healthy volunteers were imaged using a GE Signa HDx 3.0T MRI scanner and an 8-channel knee coil. IDEAL-SPGR was done with TR/TE 16/8ms, BW $\pm$31.25kHz, 14-degree FA, 384x224 matrix, 15cm FOV, 1mm sections, 90 slices, acceleration factor 2, and 5:07 scan time. 3D-FSE-Cube used TR/TE 2220/24ms, BW $\pm$31.25kHz, ETL 44, 256x256 matrix, .5 NEX, 15cm FOV, .7mm sections, 200 slices, fat-saturation, acceleration factor 3.48, and 5:00 scan time. VIPR was acquired with TR/TE 3.6/.3ms, BW $\pm$125kHz, 15-degree FA, 384x384x384 matrix, 1 NEX, 15cm FOV, 5:00 scan time, and 3-slice averages in sagittal, axial, and coronal planes to obtain .39x.39mm in-plane resolution and 1.2mm sections. Signal-to-noise ratio (SNR) was measured in cartilage and joint fluid, and fluid/cartilage cartilage-to-noise ratio (CNR) was calculated. SNR and CNR values were normalized to account for differences in voxel size. Cartilage volume was measured by segmentation with OsiriX (version 2.7.5). Each variable was analyzed by the Friedman test and a post-hoc paired t-test. Statistical signficance was indicated by a p-value less than .05.

RESULTS: VIPR had comparable cartilage SNR (20.9$\pm$1.9) to IDEAL-SPGR (22.7$\pm$4.0, $p>.1$) and 3D-FSE-Cube (19.4$\pm$2.3, $p>.1$). IDEAL-SPGR yielded higher cartilage SNR than 3D-FSE-Cube ($p<.01$), likely due to its shorter TE. VIPR produced the greatest fluid SNR (50.3$\pm$5.8), followed by 3D-FSE-Cube (36.9$\pm$8.2) and IDEAL-SPGR (8.8$\pm$1.6), with related $p<.001$. VIPR yielded CNR (29.4$\pm$6.1, $p<.001$) that was higher than the comparable CNR values of 3D-FSE-Cube (17.5$\pm$7.8) and IDEAL-SPGR (13.9$\pm$3.6, $p>.2$). VIPR, 3D-FSE-Cube, and IDEAL-SPGR all produced equivalent volume measurements of the femoral, tibial, and patellar cartilage (Friedman test, $p>.4$).

CONCLUSION: VIPR and 3D-FSE-Cube replicate the advantage of 3D-SPGR by providing accurate volume measurements. VIPR and 3D-FSE-Cube have SNR and CNR comparable to IDEAL-SPGR, while also displaying the bright synovial fluid characteristic of 2D-FSE; this bright fluid may highlight cartilage surface defects and may allow for diagnosis of ligament and meniscal pathology. VIPR and 3D-FSE-Cube have great promise for a more rapid evaluation of OA in the knee, saving time with their single isotropic acqusition, as opposed to the multiple acqusitions of 2D-FSE. Future studies will test the accuracy of VIPR and 3D-FSE-Cube in evaluating osteoarthritic cartilage as well as ligaments, menisci, subchondral bone, and tendon using semi-quantitative scoring methods.

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Effect of sub optimal subject positioning and x-ray beam alignment on the measurement of radiographic joint space width: analysis of longitudinal data from the Osteoarthritis Initiative (OAI)

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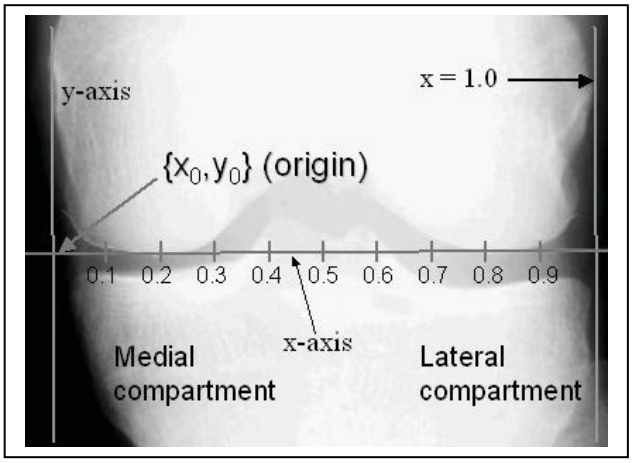
INTRODUCTION: Bilateral knee radiographs acquired using a fixed flexion protocol may have inconsistent beam angle and knee flexion from baseline to follow-up, which may affect radiographic JSW measurement.



OBJECTIVE: To study the effect of inconsistent knee flexion and beam angle alignment on the measurement radiographic joint space width (JSW) for longitudinal assessment of knee OA.

METHODS: Baseline and Year 1 knee radiographs of 160 subjects from the Progression subcohort of the Osteoarthritis Initiative (OAI) were analyzed using a software technique that measured the radiographic joint space width (JSW). The data were a subset of OAI Image Releases 0.1.1, 0.B.1, and 1.B.1.

Measurements of medial compartment minimum JSW (mJSW) and JSW at fixed locations were made by a semi-automated software tool that delineated the femoral and tibial margins of the joint. Measures of JSW were defined as the distance from the tibial margin to the femur margin at fixed locations on the coordinate system shown in Figure 1. In a previous study it was determined that the most longitudinally responsive location for measuring JSW was at x = 0.25.

To assess changes in tibial plateau angle between baseline and follow-up, we calculated the distance between the tibial rim and tibial plateau on the digitized image at the location x = 0.2 according to the coordinate system at both visits. Ball bearings placed on the frame, allowed for the measurement of the x-ray beam angle at the joint line at each visit, and the change in angle between visits,. We used a software method to measure the change in beam angle between baseline and follow-up for 115 subjects. For the remainder of the knees, our automated method was not able to determine the beam angle at one or both visits, due to software failures and poor quality images

Using linear regression, we tested the hypotheses that there were associations between change in JSW between baseline and follow-up and the change in rim alignment and the change in beam angle.

	R	Significance
Change in mJSW vs rim alignment (N = 160)	0.053	p=0.25
Change in JSW(x=0.25) vs rim alignment (N = 160)	0.053	p=0.025
Change in mJSW vs beam angle (N = 115)	0.003	p=0.49
Change in JSW(x=0.25) vs beam angle (N = 115)	0.075	p=0.21

RESULTS: Linear regression (Table 1) showed that there was no association between either change in tibial rim alignment or change in beam angle and the change in JSW.

CONCLUSIONS: We found that increases in the measured JSW from baseline to a one year follow-up did not appear to be due to inconsistent subject positioning or x-ray beam angle. The results imply that post acquisition correction for subjects with inconsistent flexion and beam angle may not improve the JSW accuracy. The data also suggest JSW measurements, using the fixed flexion technique and the positioning frame, are robust to changes in subject positioning and beam angle.

Study of location specific lateral compartment radiographic joint space width for knee osteoarthritis progression: analysis of longitudinal data from the Osteoarthritis Initiative (OAI)

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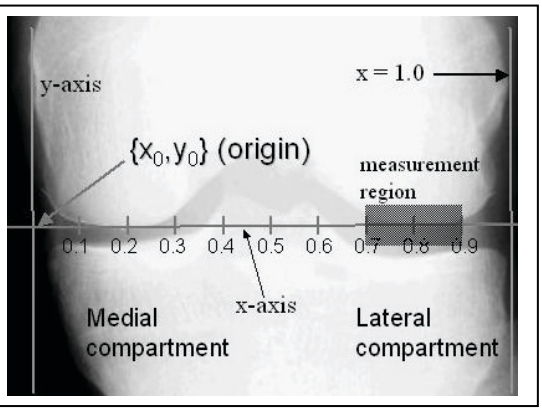
INTRODUCTION: Lateral compartment JSW is a potentially important measurement for subjects with lateral compartment OA, and as a measure of pseudowidening for medial compartment disease.



OBJECTIVE: To study location-specific radiographic joint space width (JSW) in the lateral compartment.

METHODS: Baseline and Year 1 knee radiographs of 100 subjects from the Progression Cohort of the Osteoarthritis Initiative (OAI) were analyzed using a software technique that measured the radiographic joint space width (JSW). The data were a subset of OAI Image Releases 0.1.1, 0.B.1, and 1.B.1. Radiographic JSW and the baseline varus-valgus anatomical alignment angle were measured on a single indexed knee for each subject.

Measures of JSW were defined as the distance from the tibial margin to the femur margin at fixed locations on the coordinate system shown in Figure 1. JSW was measured at nine fixed locations from x = 0.7 to x = 0.9. A subset of 40 subjects were defined as having lateral compartment OA based on an anatomical angle of greater than 2 degrees valgus. Lateral compartment minimum JSW (mJSW) was also measured for this subset. The remaining 60 subjects were defined as having medial compartment OA. The average and standard deviation of the JSW loss, and the standardized response means (SRMs) are reported.

	Gain (mm)	SD (mm)	SRM
JSW(x=0.7)	-0.01	0.82	-0.01
JSW(x=0.725)	-0.01	0.68	-0.01
JSW(x=0.75)	-0.03	0.70	-0.05
JSW(x=0.775)	0.02	0.65	0.04
JSW(x=0.8)	0.03	0.69	0.05
JSW(x=0.825)	0.08	0.65	0.13
JSW(x=0.85)	0.10	0.63	0.16
JSW(x=0.875)	0.12	0.63	0.19
JSW(x=0.9)	0.09	0.63	0.14

Table 1

	Loss (mm)	SD (mm)	SRM
JSW(x=0.7)	0.18	0.58	0.30
JSW(x=0.725)	0.14	0.55	0.25
JSW(x=0.75)	0.11	0.56	0.19
JSW(x=0.775)	0.11	0.61	0.19
JSW(x=0.8)	0.10	0.55	0.18
JSW(x=0.825)	0.09	0.53	0.16
JSW(x=0.85)	0.09	0.59	0.15
JSW(x=0.875)	0.10	0.59	0.18
JSW(x=0.9)	0.10	0.58	0.17
mJSW	0.12	0.50	0.25

Table 2

RESULTS: Table 1 provides measurements of JSW gain for the 60 subjects defined as having medial compartment OA. Increased lateral compartment JSW is observed for locations in the outer portion of the joint (higher x value). Table 2 gives the results for the 40 subjects defined as having lateral compartment OA. Here, decreased JSW is evident for locations in the more central portion of the joint (lower x value).

CONCLUSIONS: The results in Table 1 indicates that joint widening in the lateral compartment occurs for subjects with medial compartment OA. The observation of greater JSW loss in the central portion of the joint for lateral OA (Table 2) was similar to results reported for medial compartment OA. This effect may also be due to the difficulty in determining a consistent tibial plateau in the outer portion of the lateral compartment.

Radiographic lateral compartment JSW is a potentially important metric for assessing knee OA for both lateral and medial compartment disease. Determining precise mJSW in the lateral compartment can be difficult due to sub optimal positioning. Location specific JSW permits a measurement of JSW for all subjects and may provide a superior measure of OA progression.

KNEES WITH X-RAY JOINT SPACE NARROWING HAVE GREATER MR-BASED CARTILAGE LOSS – DATA FROM THE OSTEOARTHRITIS INITIATIVE (OAI)

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INTRODUCTION: It is currently unclear whether cartilage loss is greater in knees with advanced stages of radiographic OA (i.e. knees that display radiographic joint space narrowing [JSN]) than in knees with earlier stages of radiographic OA, where no JSN is yet apparent.

OBJECTIVE: To examine whether knees with greater radiographic JSN at baseline display greater cartilage loss (as measured quantitatively with MR imaging) over 1 year than knees without JSN at baseline.

METHODS: The subsample studied was drawn from 2678 cases from the OAI (public-use datasets 1.2.1 Clinical Data set and 1.B.1 Imaging Data set), a multi-center, longitudinal cohort study designed to identify biomarkers for the development and progression of symptomatic knee OA. Patients were selected to fulfill the following criteria: bilateral frequent pain (both knees), BMI>25, medial JSN (OARSI grade 1-3) in one knee, but no or less JSN in the contra-lateral knee, and no (or less) JSN in the lateral (than in the medial) compartment. The knees were initially selected based on radiographic status of the site readings in fixed flexion radiographs and were re-read centrally to confirm unilateral medial JSN. 80 participants met the eligibility criteria (32 men, 48 women; age= 60.6±9.1 yrs. [mean ± SD]; BMI= 31.1±4.0). Of these, 73 were JSN 0 and 7 medial JSN 1 in the less affected knee, whereas 47 were medial JSN 1, 25 JSN 2, and 8 JSN 3 in the more severely affected knee. Baseline and year 1 follow-up sagittal DESSwe MR images of both knees (0.7mm slice thickness) were obtained on 3T Siemens Trio scanners. 7 experienced readers segmented the medial tibial (MT) and medial femoral condylar (MF) cartilage, with blinding to the order of acquisition. All segmentations were quality controlled by one reader (S.M.). The mean cartilage thickness over the entire subchondral bone area (ThCtAB) was computed using proprietary software. The femoral condyle was separated into a weight-bearing (cMF) and posterior part (pMF) at 75% between the trochlear notch and the posterior end of the femur. The mean change (MC%), SD of change, standardized response mean (SRM = MC/SD) of ThCtAB were calculated in these regions of the medial femorotibial compartment

RESULTS: Whereas knees without JSN showed relatively little progression in the medial tibia (MT) and femur (cMF & pMF), knees with JSN (1-3) tended to display a higher rate of cartilage loss (Table 1). The rate and SRM of cartilage loss was higher in knees with worse grades of JSN (Table 1). In knees with grade 2/3 JSN, the change was higher in cMF than in MT (p=0.01) and than in pMF (p=0.08). The highest sensitivity to change was observed in the weight-bearing femur (cMF) of the JSN 2/3 knees (n=33; mean change = -7.9% p.a.; SRM=-0.74; Table 1).

Table 1: Cartilage loss in the medial femoro-tibial compartment of 160 knees as a function of JSN at baseline.

		MT		cMF		pMF	
		MC%	SRM	MC%	SRM	MC%	SRM
JSN 0	(n=73)	-1.0%	-0.33	-1.0%	-0.16	0.0%	-0.00
JSN 1	(n=54)	-1.9%	-0.34	-1.8%	-0.15	-1.2%	-0.23
JSN 2/3	(n=33)	-3.6%	-0.54	-7.9%	-0.74	-3.3%	-0.63

CONCLUSION: Knees with JSN at baseline display greater cartilage loss (by quantitative MRI) than those without, and the rate and sensitivity to change of cartilage loss increases with worse JSN (1-3). The results suggest that MRI-based measures of cartilage morphometry are particularly responsive at the later stages of OA.

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ACKNOWLEDGMENT: OAI investigators and technicians and Chondrometrics GmbH technicians for segmentation.
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FORUM ABSTRACT FOR THE WORKSHOP ON IMAGING-BASED MEASURES OF OSTEOARTHRITIS

Abstract

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The Canadian Arthritis Network's Unique Model of Consumer Involvement in Research

This power point presentation focuses on the model used for the involvement of consumers in arthritis research funded by the Canadian Arthritis Network (CAN).

The presentation provides the audience with an overview of all areas where Canadian consumers are involved in CAN and begins with its governance structure – where consumers are voting members of all operating committees of CAN. It will also present an overview of the membership of the Consumer Advisory Council (CAC): who they are, their strengths, their skills, their experiences and, finally, demonstrate that CAC members have informal and formal networks and that they speak “street arthritis”.

The presentation then explains the benefits of including consumers in research in CAN from the consumers point of view. They are as follows:

- Benefits to the Canadian society
- Benefits to the arthritis research community
- Benefits to the arthritis consumer community
- Benefits to the Canadian government

Next the presentation offers some examples of what consumers have done as consultants, as collaborators and as co-investigators in research projects.

This is followed by a brief overview of the work in progress to improve consumer participation in research in CAN.

The presentation ends by providing a picture of the consumer networks that exist in Canada and how the consumers interact with CAN investigators and trainees and also with other Canadian arthritis-related organizations and with international organizations and how these organizations interact with each other.

The presentation runs about 8 - 10 minutes

SPONSOR: Canadian Arthritis Network, Toronto, Canada
DICLOSURE STATEMENT: This presentation is a collaborative effort
ACKNOWLEDGMENT: Jean Légaré and other CAC members
CORRESPONDENCE ADDRESS: Elliott.marg@gmail.com

CONSUMERS: EQUAL PARTNERS IN RESEARCH

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INTRODUCTION: Background**:** The Canadian Arthritis Network (CAN) was established in 1998 and is currently one of 21 Network Centres of Excellence funded by the Canadian government. CAN is unusual in its structure, governance and research mandate due to its full inclusion of people with arthritis, allowing them full voting rights on all of its committees as well as a vote in decisions related to its funded research. To satisfy CAN's mandate, the Consumer Advisory Council (CAC) was formed in 2002. Dr. Robin Poole, the Network's recently retired Scientific Director, stated, "CAN is unique in the world because we involve, as equal partners, people with arthritis, the pharmaceutical and biotechnology industries, government and non-governmental organizations in the development, conduct and implementation of our research in the marketplace, thereby ensuring its relevance and application."1

OBJECTIVE: The Canadian Arthritis Network (CAN) provides an excellent model for successful consumer involvement in all aspects of arthritis research. CAN's integration of the Consumer Advisory Council (CAC) at all decision making levels is an innovative Canadian model that is easily transferable to other disease-related research arenas.

METHODS: The CAC is comprised of a diverse membership, people who volunteer their time and represent a wide range of professional experience, age, culture, language, geographic region and types of arthritis. The members of the CAC are selected for their commitment to excellence in arthritis research. They participate in CAN in several ways They are Research Advisors, Policy Advisors, Consumer Reviewers, Knowledge Brokers, as well as Co-Presenters at Conferences & Symposiums. Also included on the Council are various Associate Members, volunteers from other Canadian Arthritis patient organizations that share an interest in Research. These include The Canadian Arthritis Patient Alliance (CAPA) and Patient Partners in Arthritis, The Cochrane Collaboration, and The Arthritis Society.

RESULTS: Consumers identify research priorities that are directly in line with the needs of people living with arthritis as well as comment on the relevance of proposed studies.Dr. Marc Pouliot, at the Université Laval in Quebec has stated, "By understanding how consumers feel pain, I can target my research to the specific area that will help the most." Researchers also benefit from consumer involvement in Knowledge Transfer and Exchange. Consumers have developed a universal template that researchers can use for lay summary outlines. Research results can be widely disseminated using the vast consumer networks that also provide an extensive feedback mechanism. CAC members are actively involved in consumer partner organizations and many other collaborative initiatives, locally, regionally, nationally & internationally. They can also comment on, with knowledge, public policy related to all aspects of evidence-based health care delivery as well as best practise issues related to clinical trials.

CONCLUSION: Consumer participation increases the legitimacy of health research which is primarily pursued for the benefit of the public. The principle of democracy and the right to participate must be involved in all decisions that directly affect the health and lives of consumers.3 Their knowledge and experience in relation to their disease is invaluable.The Network of Centres of Excellence Secretariat wrote in their report, "the integration of the Consumer Advisory Council at all decision-making levels is forward thinking and could be an inspiration to all other Networks of Centers of Excellence."4 The CAC of CAN is certain that in order to ensure the relevance of any research, ensure the research results are broadly disseminated, ensure the results are implemented in current health care policies, and ensure that unmet needs are addressed by the research community; consumers must be an integral part in all aspects of any research organization..

SPONSOR: The Canadian Arthritis Network
ACKNOWLEDGMENT: References: 1. Dr. Robin Poole. Canadian Arthritis Network 2005 Renewal Application. P. 1. 2. Dr. Marc Pouliot. Centre de Recherche en Rhumatologie et Immunologie, Universite Laval, Quebec, Canada 3. Caron-Flinterman, J.F., J.E.W. Broerse, J.F.G.Bunders. "The experiential knowledge of patients: a new resource for biomedical research?" in Social Science and Medicine 60 (2005) 2575-2584. 4. Networks of Centres of Excellence Selection Committee Report, July 2004.
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THE ACUTELY ACL INJURED KNEE ASSESSED BY MRI: MORPHOMETRIC CHANGE OF CARTILAGE OVER THE FIRST TWO YEARS AFTER INJURY

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INTRODUCTION: The central medial femur (cMF) and trochlea femur (TrF) were suggested to be regions sensitive to change in cartilage morphology after ACL injury, based on 1 year follow-up. Longer term changes are not known.

OBJECTIVE: To investigate morphometric change of cartilage in cMF and TrF over the first two years after acute ACL injury.

METHODS: In this longitudinal MRI analysis we assessed a consecutive sub-set of subjects included in an RCT of surgical versus non-surgical treatment after acute ACL injury (The KANON study). 29 patients (29 knees, 21 males) with a not more than 4 weeks old ACL rupture were assessed by MRI and underwent similar extensive rehabilitation. 19 of these subjects (mean age 28, 95%CI, 26-30 y) in addition underwent an ACL reconstruction within 7 w from injury, while 10 (mean age 25, 95%CI 21-29 y) were treated with rehabilitation alone. MRI scans were performed using a 1.5 T imager with a circular polarized surface coil at baseline, 3 and 24 months after injury. A quantitative analysis was performed where a multi-spectral image data set was created and computer analyzed. To avoid artefact bias (i.e. fixation material in group treated with ACL reconstruction), change was measured from 3 to 24 months. We quantified cartilage volume (VC), thickness (ThCcAB) and surface area (AC) in cMF and TrF. Change was reported as mean change, percent change and standard response mean (SRM, mean change divided by the standard deviation of change).

RESULTS: In cMF, cartilage morphometry measures increased from 3-24 months after injury (0.052<SRM>0.750). Mean cartilage thickness and volume increased with 4.2% (95%CI, 2.1-6.3) and 4.5% (1.8-7.2) respectively. Thickness increased more in knees treated with ACL reconstruction than in knees treated with rehabilitation alone, 5.6% (2.8-8.4) and 1.6% (-1.3-4.4), respectively. In TrF, mean measures decreased (-0.430<SRM>-0.133). AC of TrF decreased (2.7%, 1.2-4.2) in knees treated with ACL reconstruction but increased (1.2%, -0.4-2.7) in those treated with rehabilitation alone (Table 1).

CONCLUSION: Cartilage hypertrophy of cMF, indicated by increased ThCcAB and VC, occurs during the first 24 months after ACL injury. An early ACL reconstruction appears to be associated with morphometric change of cartilage in cMF and TrF after 2 years, where SRMs close to 1 were observed.

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	All subjects (N=29)			Rehab alone (n=10)		ACL reconstruction (n=19)	
	Change mean (95%CI)	Change % mean (95%CI)	SRM	Change mean (95%CI)	SRM	Change mean (95%CI)	SRM
AC (mm^2)							
cMF	1.8 (-11.5, 15.0)	0.4 (-1.1, 1.8)	0.052	-3.7 (-26.9, 19.6)	-0.114	4.6 (-13.0, 22.2)	0.126
TrF	-32.0 (-60.3, -3.7)	-1.4 (-2.6, -0.1)	-0.430	24.0 (-6.4, 54.3)	0.566	-61.4 (-95.6, -27.1)	-0.864
ThCcAB (mm)							
cMF	0.09 (0.04, 0.14)	4.2 (2.1, 6.3)	0.750	0.03 (-0.03, 0.1)	0.333	0.12 (0.06, 0.18)	0.923
TrF	-0.02 (-0.08, 0.04)	-0.5 (-2.9, 1.8)	-0.133	0.02 (-0.02, 0.07)	0.286	-0.04 (-0.13, 0.04)	-0.235
VC (mm^3)							
cMF	65.4 (17.8, 113.0)	4.5 (1.8, 7.2)	0.522	16.0 (-39.0, 71.1)	0.208	91.4 (24.3, 158.4)	0.657
TrF	-88.5 (-215.0, 37.9)	-1.2 (-3.9, 1.5)	-0.267	71.1 (-27.3, 169.5)	0.517	-172.6 (-353.4, 8.3)	-0.460

Table 1. Mean change of cartilage surface area (AC), thickness (ThCcAB) and volume (VC) between 3 and 24 months (95%CI) after ACL injury, mean change in percent (95%CI) and SRM.

REPEATABILITY OF *IN VIVO* SODIUM MRI OF CARTILAGE IN EARLY OA

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INTRODUCTION: Early degenerative changes in articular cartilage are accompanied by glycosaminoglycan (GAG) depletion in the cartilage matrix. Sodium MRI has been shown to correlate with GAG concentration, and may be useful in detecting and tracking early GAG depletion. This could be helpful for drug discovery in osteoarthritis. Sodium MRI is challenging due to relatively low ^{23}Na concentrations in biological tissues, rapid signal decay, and a low gyromagnetic ratio. Despite these challenges, improved coils and gradient hardware coupled with higher field strengths enable diagnostic-quality sodium MRI *in vivo* in reasonable scan times.

OBJECTIVE: To measure the repeatability of sodium MRI in the patella at 3.0T in early OA subjects.

METHODS: A fast gradient-spoiled sequence using the 3D cones k-space trajectory and a rapid RF excitation was developed for sodium image acquisition. The centric 3D cones trajectory permits short echo times and achieves very high SNR efficiency, while providing a relatively smooth k-space weighting and making efficient use of gradient resources. The sodium sequence was implemented on a 3T GE Signa Excite whole-body scanner. We used a custom sodium-tuned transmit/receive 3" surface coil.

Scan parameters at 3T were: TR = 50 msec, FOV = 16x16x12.8 cm^3, matrix = 128x128x32 (1.25x1.25x4 mm^3 resolution), 8 ms readout, and 16 signal averages for a total scan time of 16 min. The transmit gain was set manually during prescan to select a flip angle that maximizes signal at the given TR, and was held constant during all acquisitions.

The patellofemoral cartilage was imaged in ten knees of subjects with early OA (ages 33-54) on consecutive days. Early OA was determined by a radiographic or MRI findings of osteophytes. The skin was marked and the subject returned the following day for a repeat scan in the same relative position of the patella and surface coil. Cartilage signal was measured manually by drawing ROI's on the medial and lateral facets of the patella cartilage. SNR was then measured across for ROI by dividing cartilage signal by the standard deviation of the noise. SNR was compared at the two days for each facet, and the coefficient of variation was calculated (Figure 1).

RESULTS: Figure 2 summarizes the coefficient of variation of the SNR measurements in the medal facet of the patella cartilage. The coefficient of variation ranged from 1 to 7 %, and the overall average was 6%. Results in the lateral facet were similar to the medial facet.

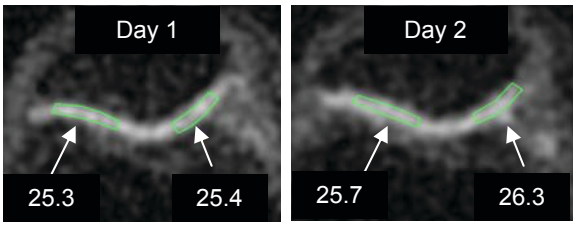

Figure 1: Sodium SNR measurements in the patella cartilage on two consecutive days in a subject with early OA.

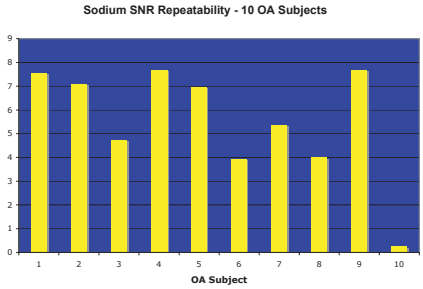

Figure 2: Sodium repeatability in the medial facet in the patella cartilage on consecutive days.

CONCLUSION: Measurement of sodium reproducibility in patella cartilage at 3T is possible with an acceptable coefficient of variation even with a surface coil. Recent developments of a volume coil for whole-knee imaging and B1 mapping methods will further improve repeatability and utility of sodium MRI.

SPONSOR: 1R01-EB002524, 1R01-EB005790, Glaxo-Smith-Kline
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TWO YEAR LONGITUDINAL CHANGES IN REGIONAL CARTILAGE MORPHOLOGY IN A MULTICENTER, MULTIVENDOR MRI STUDY AT 3.0 T- THE A9001140 STUDY

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INTRODUCTION: We have previously reported relatively small changes in cartilage thickness at total femorotibial cartilage plate level in an enriched OA population (i.e., obese women with KLG 2 and 3) over 1 year in a multicenter, multivendor MRI study at 3.0T. Subregional analysis revealed that the sensitivity to change in the external and central subregions of the medial tibia (MT), and in the central area of the weight-bearing (central) medial femur (cMF) was greater than at total plate level.

OBJECTIVE: To compare annual rates of cartilage loss over 1 and 2 years, and to investigate whether the regions with the highest sensitivity to change observed over 2 years are the same as those over 1 year.

METHODS: 1.0mm coronal FLASHwe MR images of the knee were acquired at baseline, 12 months and 24 months in 148 female participants at 7 clinical centers with Siemens and GE 3.0T scanners. 90 participants had no symptoms and no evidence of radiographic OA; 58 had medial femorotibial OA on conventional standing AP radiographs (30 KLG 2 and 28 KLG 3). Baseline and follow up images were read as pairs, with blinding to order of acquisition.. The mean cartilage thickness over the entire subchondral bone area (tAB) was computed (ThCtAB). Subregional cartilage thickness was determined for central (20% of the tAB), anterior, posterior, external and internal subregions of the medial (MT) and lateral tibia (LT), and for central (33% of the tAB), external and internal subregions and the weight-bearing medial (cMF) and lateral femur (cLF), using proprietary software (Chondrometrics). A false discovery rate of 0.1 was applied to p-values.

RESULTS: At 2 years, significant decreases in the ThCtAB were observed in control subjects (KLG 0) in the anterior and central subregions of the MT (SRM=-0.26 and -0.27, respectively) (Table 1). In KLG 2 participants, the reduction in ThCtAB in MT was similar to healthy subjects and a significant increase was observed in the ThCtAB in the external subregion of cMF (SRM=0.52). In KLG 3 participants, changes appeared larger in cMF (-2.1%) than in MT (-1.4%) but the highest SRMs were observed in MT. eMT and cMT displayed the relatively greatest changes in MT (SRM= -0.53 and -0.57, respectively). Consistent with the 1 year data, the greatest annual reductions in ThCtAB (2 to 4%) were observed in the KLG3 subjects in both MT and cMF. The greatest reduction in ThCtAB was observed in the central and external subregions of MT (SRM=-0.53 and -0.57).

Table 1: Annual rates of change in cartilage thickness (ThCtAB) observed over a 2 year period

ANNUAL RATE	KLG 0 (n=90)		KLG 2 (n=30)		KLG 3 (n=28)	
	MC%	SRM	MC%	SRM	MC%	SRM
MT	-0.31	-0.23	-0.32	-0.19	-1.41*	-0.59
Central MT	-0.50*	-0.27	-0.60	-0.25	-2.10*	-0.53
External MT	-0.37	-0.18	-0.52	-0.19	-3.85*	-0.57
Internal MT	0.06	0.03	-0.53	-0.26	-0.59	-0.29
Anterior MT	-0.53*	-0.26	0.06	0.02	-1.20	-0.32
Posterior MT	-0.08	-0.04	-0.03	-0.02	-0.03	-0.02
cMF	-0.19	-0.10	0.47	0.31	-2.10	-0.34
Central cMF	-0.37	-0.15	0.21	0.09	-2.99	-0.35
External cMF	0.30	0.14	1.23*	0.52	-3.30	-0.34
Internal cMF	-0.34	-0.15	0.17	0.08	-0.57	-0.18

MC%=mean change, SRM=standardized response mean; *=statistically significant change

CONCLUSION: As over one year, the annual rate of cartilage loss in MT exceeded that in cMF in KLG 2 subjects. However, over 2 years the KLG 2 participants did not show greater changes than healthy controls and iMT showed a similar change as eMT. In KLG 3 subjects, the annual rate of cartilage loss was greater in cMF than in MT at 1 year and 2 years, but over 2 years the highest SRMs were observed in eMT and cMT rather than ccMF.

SPONSOR: Pfizer Global Research and Development, New London, CT, USA.
DISCLOSURE STATEMENT: F.E. consults for Pfizer, Merck Serono and Wyeth
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TOWARD AUTOMATIC ARTICULAR CARTILAGE SEGMENTATION FROM MRI: DISTANCE CONSTRAINED SEGMENTATION

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INTRODUCTION: Accurate segmentation of articular cartilage is important for MRI-based diagnosis and therapy of cartilage diseases, e.g., osteoarthritis. Fully automatic segmentation is desired since it is both time- and cost-efficient. The automatic segmentation of articular cartilage is challenging because the contrast between cartilage and some surrounding tissues could be too poor to distinguish them. We report a distance constrained method to address the difficulty. In MR images of knee, the contrast between bone and cartilage is usually excellent. Hence the Bone and Cartilage Interface (BCI) is relatively easy to detect. Then the distance from the cartilage surface to the bone is used as a constraint to segment cartilage when contrast cannot provide enough information for segmentation.

OBJECTIVE: Our objectives are to provide approximate segmentation when 1) the contrast between cartilage and surrounding soft tissue is poor; 2) the cartilages contact each other and no obvious contrast exists in the contact interface.

METHODS: 32 clinical 3D knee images were acquired on a Philips Achieva system. Matrix sizes were 320×320×170 or 512×512×64. Bones were segmented by in-house fully automatic segmentation algorithm, and corresponding BCIs were found using directional gradient. Distance functions were calculated with the segmented bone. These distance functions define the distance from any point to the bone. Gradient was used to search the cartilage surfaces. Segmentation based on thickness smoothness when no contrast is available: When there was no sufficient contrast, i.e. very low gradient, it is assumed that the distances from cartilage surface to the bone, i.e. cartilage thickness, change gradually. Hence the thicknesses for regions without sufficient contrast can be approximated with the knowledge of surrounding cartilage thickness. Separation of attached cartilages: If there is no contrast between two attached cartilages, segmentation based on thickness smoothness is first applied. However, it is possible there are still overlaps of these two cartilages. The distances to bones are used to divide them. For a point in the intersection, the distance to each bone can be found by checking the calculated distance function. This point is assigned to the nearer bone.

RESULTS: All 32 data sets were automatically segmented using the proposed method. 14 data sets were manually segmented. The automatic segmentations were evaluated using the manual segmentations as golden standard. Constrained by the distance to bone, accurate segmentation was generated when there is no strong contrast available; the attached cartilages were also accurately divided in all data sets. One example is shown in Figure 1. Yellow curves are for manual segmentation, while red curves are for automatic segmentation. Based on the results of 14 data sets, the sensitivity and specificity were 88.9% ± 0.03% and 99.8% (Femur), 86.6% ± 0.03% and 99.9% (Tibia), and 86.7% ± 0.03% and 99.9% (Patella). Truncation of sharp corners of cartilages can be observed in automatic segmentations.

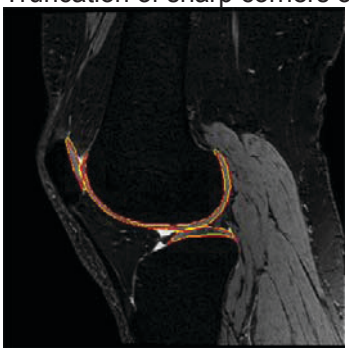

Figure 1

CONCLUSION: The assumption of the gradual change of cartilage thickness provides reasonable segmentation at locations without enough contrast. The division of attached cartilages based on distance to bones also generated accurate results. Next steps include improve the segmentation of cartilage corner, and combine MR phase information for segmentation.

DICLOSURE STATEMENT: F. Huang is an employee of Invivo corp.

ACKNOWLEDGMENT: Dr. Clemens Bos from Philips Healthcare is to be thanked for providing the data and invaluable comments. Dr. Sebastian Dries from Philips Research is to be thanked for providing the manual segmentation.

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CARTILAGE MORPHOMETRY REGION OF INTEREST ANALYSIS; BY SELECTING REGIONS WITH DENUDED AREAS CAN WE DETECT GREATER AMOUNTS OF CHANGE?

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INTRODUCTION: Based on recent analyses the short-term responsiveness of MRI derived cartilage morphometry parameters may not be as good as we had hoped. We sought to ascertain if by selecting regions of interest with already denuded cartilage the remaining cartilage within this region of interest was susceptible to greater rate of change in cartilage morphometry measures.
METHODS: Subjects included for this analysis are a subset of the approximately 4700 participants in the OAI Study. Bilateral radiographs and 3T MRI (Siemens Trio) of the knees and clinical data are obtained at baseline and annually in all participants.150 subjects from the OAI Progression subcohort all of whom had both frequent symptoms and, in the same knee, radiographic OA (ROA) based on a screening reading done at the OAI clinics were eligible for this exploratory analysis. One knee from each subject was selected for analysis. Using sagittal 3D DESSwe MR images from the baseline and 12 follow-up month visit, a segmentation algorithm was applied to the cartilage plates of the index knee to compute the cartilage volume, normalized cartilage volume (Volume normalized to bone surface interface area), and percent denuded area (Total Cartilage Bone Interface area denuded of cartilage). Summary statistics of the changes (absolute and percentage) from baseline at one year and the standardized response mean (SRM), i.e. mean change divided by the standard deviation change were calculated. Analyses are stratified into three groups according to baseline assessment of denuded area: those with no denuded area in the region of interest at baseline, and then 2 groups (small denuded area and larger denuded area) of equal sample size.
RESULTS: On average the subjects were 60.9 years of age and obese with a mean BMI of 30.3 kg/m^2. The table below depicts the results of the analyses in the three strata for both cartilage volume and normalized cartilage volume.

	No denuded surface area			**Less denuded surface area**			**More denuded surface area**			**p value for F Test**
	n	**Mean Change (SD)**	**SRM**	n	**Mean change (SD)**	**SRM**	n	**Mean change (SD)**	**SRM**	
Cartilage Volume Trimmed (mm^3)										
Cent Med Femur	101	-36.0(101.3)	-0.36	24	-43.2(118.8)	-0.36	25	-32.6(96.9)	-0.34	0.93
Cent Med Tibia	111	-0.6(80.9)	-0.00	19	-56.0(103.3)	-0.54	20	-14.07(50.6)	-0.28	0.02
Cent Med F+T	97	-37.5(155.8)	-0.24	26	-68.2(218.7)	-0.31	27	-55.9(123.3)	-0.45	0.66
Normalized Cartilage Volume Trimmed (mm)										
Cent Med Femur	101	-0.02(0.21)	-0.08	24	-0.11(0.21)	-0.54	25	-0.06(0.14)	-0.46	0.08
Cent Med Tibia	111	0.01(0.11)	0.07	19	-0.13(0.20)	-0.65	20	-0.02 (0.09)	-0.23	<.0001
Cent Med F+T	97	-0.01(0.28)	-0.03	26	-0.15(0.36)	-0.43	27	-0.12(0.27)	-0.45	0.04

CONCLUSION: By selecting participants with the presence of full thickness cartilage defect and increasing denuded area the ability to demonstrate change in cartilage loss is markedly improved. This option for screening during recruitment in clinical trials could facilitate the detection of participants at greater risk of subsequent cartilage loss.

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DICLOSURE STATEMENT:
ACKNOWLEDGMENT: The participants and staff of the OAI Study.
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RELATION OF REGIONAL ARTICULAR CARTILAGE MORPHOMETRY AND MENISCAL POSITION BY MRI TO JOINT SPACE WIDTH IN KNEE RADIOGRAPHS.

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for the A9001140 Investigators

INTRODUCTION: The objective of this analysis was to ascertain the contribution of articular cartilage morphometry and meniscal position on MRI to joint space width (JSW) measured in the Lyon schuss radiograph of the knee, and to specifically identify which subregions of tibial and femoral cartilage and which measures of the meniscus best explain variations in JSW.

METHODS: 62 obese women with knee OA and 99 non-obese female controls (mean age 56.6 yrs) were imaged at 7 clinical centers by 3T MRI. Double oblique coronal acquisitions were obtained using water excitation spoiled gradient echo sequences (1.0x 0.31x 0.31mm^3 resolution). Segmentation of femoro-tibial cartilage morphology was performed using Chondrometrics GmbH software. Meniscal position (subluxation and % coverage of the medial tibial plateau) was measured in sagittal and coronal planes (EFilm software). Minimum medial joint space width (mJSW) was measured by computer in the Lyon Schuss knee radiograph; Kellgren and Lawrence grades (KLG) were assigned on standing anteroposterior knee films. The relative contribution of regional cartilage thickness and meniscal position to mJSW was assessed initially in univariate models and subsequently with multivariable modelling.

RESULTS: 65% of the variation in mJSW was explained by KLG, regional cartilage thickness measures (central MT + central MF + external MT + posterior MT + internal MT) and meniscal coverage. Of these measures the medial tibia cartilage thickness measures (in particular central, external, and to a lesser extent the internal and posterior subregions) and central region of the weight-bearing femoral condyle (ccMF) play a consistent and small role in variations in mJSW observed across all KLG. This however explains only approximately one third of the mean difference in mJSW that exists between KLG2 subjects and those without OA (KLG0). In contrast ccMF and the addition of percent meniscal coverage to this model explains the remaining differences in mean mJSW found between those subjects with definite joint space narrowing (KLG3) and those without OA.

CONCLUSION: The variation in radiographic mJSW is best described by 5 regional cartilage thickness measures (central MT + central MF + external MT + posterior MT + internal MT) and percent meniscal coverage. The magnitude of each measures contribution differs according to radiographic severity with more variability explained by cartilage thickness of ccMF cartilage thickness and percent meniscal coverage with more severe disease. ~35% of the LS JSW is not our model with some possible explanation(s) being (a) the differences between the tibiofemoral *contact sites* in a LS view taken in about 20 degrees of flexion and an extended knee MRI, and (b) the difference in cartilage thickness with compression on *weightbearing* in the LS view but not in acquiring the MRI measurements.
SPONSOR: Pfizer
DICLOSURE STATEMENT:
ACKNOWLEDGMENT: The participants and staff of the Pfizer A900140 Study.
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Accelerated Parametric Imaging using Image Estimation Methods

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INTRODUCTION: Quantitative magnetic resonance imaging requires extensive scan times because sampling must be accomplished along both spatial and parametric dimensions. These long scan times limit the use of mapping in clinical imaging and monitoring osteoarthritis treatment trials. If all pixels in a parametric image series sampled at *n* points are independent, an n-fold increase in scan time is required. However, correlation usually exists within a series that can be exploited for acceleration.

OBJECTIVE: We aim to determine if 1) image estimation techniques could substantially accelerate parametric mapping of articular cartilage and 2) measure the inaccuracy created by the acceleration.

METHODS: We utilize a method inspired by accelerating time-resolved MRI (HYPR [1]), but subsample in the parametric dimension rather than in the temporal dimension. For example, instead of fully sampling each T2-weighted image in a parametric series, a composite image is built from subsampled data at multiple echo times and used as a constraint. Unlike the initial single iteration HYPR algorithms whose approximate nature caused some blurring, cartilage imaging requires more accuracy to evaluate the relatively thin articular surfaces. Therefore, we investigate two iterative derivatives of HYPR to improve accuracy. In the first, the composite image is iteratively altered to create consistency with the subsampled data from one echo time using the I-HYPR method [2]. In the second, the concept of compressed sensing and parallel imaging are utilized (HYPRIT) [3]. After this process is replicated to construct an image for each T2-weighting for which subsampled data is acquired, a T2 map is generated.

Fat-saturated 2D T2-weighted images were obtained at 8 echo times (8 -64 ms) using a Cartesian RARE sequence (8:36 scan time). The 256 x 256 images were acquired on a GE 3T magnet with an 8 channel knee coil. A 2:00 scan was simulated by computing a set of 60 subsampled projections from the original RARE images at each echo time and then using the iterative HYPR algorithms with three iterations to reconstruct each echo time frame. The reduction in encodings corresponded to a speedup factor of 4.2. Standard curve fitting methods generated the T2 maps for all methods.

RESULTS: Conventional and accelerated T2 maps were created for an asymptomatic subject in the sagittal plane and a subject with osteoarthritis (OA) in the axial plane through the patella. The accuracy of the accelerated T2 maps was computed by calculating the RMS error, using the conventional map as a gold standard, over 600 pixels containing cartilage. The accelerated method had an RMS error of 9.5% for the asymptomatic knee and 11.6 % for the OA knee. The minimum achievable error, which may also be considered as moderate blurring, is limited by the number of iterations which can be performed without noise amplification. Much of this amplification results from moving back and forth between k-space and the image space using gridding operators.

CONCLUSION: A method for constructing T2 maps from a set of highly undersampled images with an acceleration factor of 4 and a moderate error has been presented. While parallel MRI can also accelerate scanning, its SNR loss affects the accuracy of shorter T2 tissues. These methods preserve the SNR from a much longer acquisition by using it as a constraint. Methods for reducing gridding errors have allowed for an increased number of iterations [4] and would likely further reduce reconstruction errors in parametric imaging. We note that a similar methodology could also accelerate $T1\rho$ imaging.

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References: [1] Mistretta et al. MRM 2006. [2] O'Halloran and Fain. MRM, 2008. [3] Park et al. MRM 2005 [4] Samsonov and Block, ISMRM, Toronto, 2008.

QUANTITATIVE COMPUTED TOMOGRAPHY (QCT) SHOULD REPLACE DUAL-ENERGY ABSORPTIOMETRY (DXA) WHEN ASSESSING THE OSTEOARTHRITIC KNEE

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OVERVIEW: In-vivo imaging studies examining direct associations between increased proximal tibial bone mineral density (BMD) and knee osteoarthritis (OA) are lacking in the literature and offer conflicting increasing/decreasing results (Madsen 1994; Bruyere 2003; Clarke 2004; Karvonen 1998; Hulet 2002; Wada 2001). These conflicting results may be due to the limited two dimensional (2D) capabilities of current *in vivo* imaging tools used to assess BMD (principally dual-energy x-ray absorptiometry (DXA)), in combination with selected subchondral analysis regions containing cortical and/or trabecular bone which may both be affected differently by OA (Burr 2004). For the osteoarthritic knee, we propose usage of imaged measures of cortical and trabecular density located near the subchondral surface (<5.0mm), preferably assessed using three dimensional (3D) quantitative computed tomography (QCT).

PROBLEM: Subchondral bone located nearest to the overlying articular cartilage may play a significant role in the initiation and/or progression of OA. Specifically, cortical and trabecular bone located less than 5 mm away from the articular cartilage / subchondral bone interface (subchondral surface) offers the largest resistance to loading (Harada 1988) and are capable of adversely affecting the overlying cartilage (Brown 1984). DXA has limited capabilities for imaging the subchondral region of the tibia because: 1) DXA represents a complex 3D bony structure as a 2D projection image; 2) DXA is limited to imaging in the coronal and sagittal planes; and 3) DXA results are sensitive to patient positioning and physical size. Further, no repeatable guidelines have been established for assessing the osteoarthritic proximal tibia, resulting in a series of studies using variably sized 2D ROIs (region of interest) at various locations. Researchers have typically positioned ROIs away from the subchondral surface (> 10 mm) or used large ROIs (> 20 mm height). This is a concern because there may be a variable density transition zone located somewhere near the subchondral surface between the higher density subchondral bone and lower density trabecular bone found with OA subjects. While both the subchondral endplate and nearby trabeculae increase in thickness and imaged density with OA, trabeculae located more distal to the surface may decrease in density. Fractal signature analysis studies have shown that horizontal plates and vertical rods of trabecular bone in regions periarticular to OA affected regions are thinner than in knees without OA (Buckland-Wright 1996; Messent 2005). Various animal studies simulating secondary OA have shown decreases in periarticular trabecular bone density which precede thickening of the subchondral plate (Boyd 2000; Dedrick 1993). Trabecular bone distal to the surface may in fact be osteoporotic (Buckland-Wright 2004). Usage of poorly-placed large ROIs containing both the subchondral endplate and distal trabeculae likely contain bone experiencing both increased and decreased density, possibly canceling one another, and imaged BMD increases (or decreases) with OA are subsequently masked.

PROPOSAL: Future and (when possible) on-going DXA studies should use standardized ROI sizes and positions, and these positions should be near the subchondral surface to capture high density bone. We estimate that the transition zone is located somewhere between 2.5 and 5.0 mm from the subchondral surface, based upon previous mechanical strength and theoretical analyses (Brown 1984; Harada 1988) combined with our QCT studies assessing subchondral cortical and trabecular bone using the CT-TomasD technique, which measures subchondral density at defined depths from the subchondral surface (Johnston, OARSI/2007). Ongoing research is attempting to pinpoint the exact location of this transition zone in normal, early and late OA subjects. The 3D capabilities and assessment of both cortical and trabecular bone make QCT and CT-TomasD ideal techniques for assessing the OA knee.

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IN-VIVO AND IN-VITRO PRECISION OF COMPUTED TOMOGRAPHY TOPOGRAPHIC MAPPING OF SUBCHONDRAL DENSITY (CT-TomasD) IN THE PROXIMAL TIBIA

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INTRODUCTION: Subchondral cortical and trabecular bone mineral density (BMD) may both increase and/or decrease during different stages of osteoarthritis (OA) progression (Boyd 2000; Dedrick 1993; Brandt 1991; Buckland-Wright 2004). Dual energy x-ray absorptiometry (DXA), the most commonly used technique for assessing associations between BMD and OA, is poorly suited for analyzing both cortical and trabecular regions because because: 1) DXA represents a complex 3D bony structure as a 2D projection image; 2) DXA is limited to imaging in the coronal and sagittal planes; and 3) DXA results are sensitive to patient positioning and physical size. The objective of this study was to test the repeatability and precision of our novel imaging tool; CT-TomasD (computed tomography topographic mapping of subchondral density) on both living and cadaveric tibiae for the assessment of both subchondral cortical and trabecular bone.

METHODS: *In-Vitro Cadaveric Study:* Eight intact cadaver knees from five donors (4M:1F; age: 77+/-10) were scanned three times using using quantitative computed tomography (QCT) (Toshiba 64 Aquilion; Mindways BMD Spine Phantom; 0.5mm isotropic resolution, 0.15mSv radiation dosage). *In Vivo-Study:* Seven knees from seven subjects (2M:5F; age: 46+/-11) were scanned three times using QCT (GE Lightspeed; Mindways BMD Spine Phantom; 0.625mm isotropic resolution, 0.073mSv radiation dosage). BMD was assessed using our novel CT-TomasD technique which uses surface projections to assess both cortical and trabecular bone density at specific depths from the subchondral surface (Johnston OARSI/2007). Average BMD at normalized depths of 0-2.5mm, 2.5–5.0mm, and 5.0-10mm from the surface were assessed using CT-TomasD. Regional analyses were performed consisting of: (1) Medial & Lateral BMD, (2) M/L BMD ratio, and (2) BMD of a 10mm diameter 'max core'. The coefficients of variation (CV) for BMD values were calculated according to outlined procedures (Gluer et al. 1995).

RESULTS: Precision errors associated with the CT-TomasD methodology were small (Table 1). Coefficients of variation ranged between 1.0% and 1.7% for the entire medial and lateral tibial plateaus, 1.1% to 2.8% for the M/L BMD Ratio and 1.3% to 4.2% for the regional core analysis.

Table 1: In-Vitro (n=8) and In-Vivo (n=7) precision results.

	Medial & Lateral BMD			M/L BMD Ratio			Max Core (10mm diameter)		
	0-2.5mm	2.5-5mm	5-10mm	0-2.5mm	2.5-5mm	5-10mm	0-2.5mm	2.5-5mm	5-10mm
In-Vitro	1.2%	1.0%	1.7%	1.9%	2.4%	2.8%	1.3%	2.7%	4.2%
In-Vivo	1.0%	1.7%	1.6%	1.4%	1.3%	1.1%	2.5%	2.5%	2.4%

DISCUSSION: CT-TomasD demonstrates repeatable measures of subchondral cortical and trabecular bone density, measured in relation to defined depths from the subchondral surface. Though CT incurs a high radiation dosage compared with DXA, the low presence of radiosensitive tissues at the knee joint keeps radiation effects to a minimum. Our optimized in-vivo CT settings induce a radiation dosage of 0.073mSv, estimated using shareware software (CT-DOSE). This compares with an average exposure of 2.4 mSv of background radiation per year and approximately 0.05 mSv during a transatlantic flight from Europe to North America (UNSCEAR 2000), and 0.7 mSv for an anterior-posterior pelvic radiograph or a long-leg standing radiograph (Hart 1994, 1997). This 3D CT technique has the potential to identify and quantify changes in subchondral BMD that may be associated with OA disease progression.

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TOWARD AUTOMATIC SEGMENTATION OF KNEE ARTICULAR CARTILAGE IN OSTEOARTHRITIS INITIATIVE MRI DATA USING MACHINE LEARNING

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INTRODUCTION: One of the most important biomarkers for the progression of osteoarthritis is the morphological changes of articular cartilage. While the Osteoarthritis Initiative (OAI) project has been obtaining MRIs with multiple sequences regularly from a few thousand of patients to understand the factors that progress the morphological changes in the articular cartilage, MRI data processing (segmentation) is the major bottleneck that delays the data analysis. Here we propose a machine-learning-based automatic segmentation method of knee articular cartilage utilizing the MRIs from multiple sequences.

OBJECTIVE: To segment the articular cartilage in the MRI from multiple subjects using a support vector machine (SVM) trained with one manually segmented MRI set (gold standard).

METHODS: Four sets of MR images were obtained from an intact cadaveric knee with SPGR, b-SSFP and IDEAL-GRE (Water and Fat) sequences in a GE 3.0T machine to train a SVM. Femoral, tibial, patellar and fibular cartilage were manually segmented from the SPGR images using our custom software. The bones in the knee were also segmented (automatically) using a simple threshold based method and a few geometrical features such as the centers of femoral condyles, the patella surface facing femur and the tibial surface facing femur were detected automatically to obtain the geometrical information of the pixels relative to the bones (i.e. distance from the closest bone surface) in the MRI. For each pixel in the MRI, the gray color information from the four sets of MR images along with the geometrical information was input to the SVM to calculate a rule (training) that can separate the cartilage pixels from non-cartilage pixels. The same MR sequences were used to obtain four sets of knee MR images from two healthy volunteers. Again, for each pixel, the gray color information from MR images along with geometrical information was input to the trained SVM to be classified as either cartilage or non-cartilage based on the rule. Therefore, the pixels classified as cartilage were used to create three-dimensional models of cartilage. The accuracies of the cartilage models were quantified as sensitivity (true positive / (true positive + false negative)) and specificity (true negative / (true negative + false positive)).

RESULTS: The table on right side summarizes the sensitivities and specificities of the classification results when the MRIs from the cadaveric knee and two subjects were automatically segmented using the trained SVM with the manual segmentation of the cadaveric knee.

	Cadaveric knee	Knee of subject #1	Knee of subject #2
Sensitivity	99.2%	96.5%	88.4%
Specificity	97.8%	98.2%	98.8%

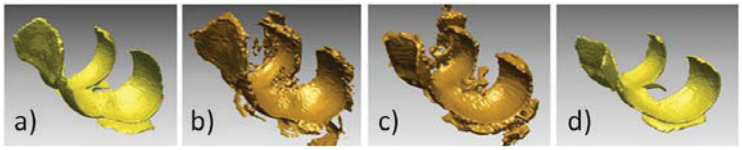

Figure 1. Cartilage models a) from manual segmentation of the cadaveric knee, b) from automatic segmentation of the cadaveric knee (self testing), c) from automatic segmentation of the knee of subject #1 and d) from manual segmentation of the knee of subject #1

CONCLUSION: The cartilage segmentation results from the subjects' knee MRIs were comparable to the segmentation of the training data (cadaveric knee) itself based on the sensitivity and specificity, which suggests that any new knee MRIs can be automatically segmented in the similar level of accuracy using this method. The MRI sequences of the OAI project were carefully chosen to provide high contrast between cartilage and non-cartilage, so this method might perform at the same or better level of accuracy with the OAI MRI Data.

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SYNOVIAL VOLUME AND BONE MARROW EDEMA ON MRI PREDICT RADIOGRAPHIC SEVERITY OF KNEE OSTEOARTHRITIS, AND CORRELATE WITH TNFα EXPRESSION IN PERIPHERAL BLOOD LEUKOCYTES

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PURPOSE: To evaluate the potential use of 3T MRI in knee osteoarthritis (OA) for correlating quantitative synovial volume (SV), cartilage, and bone marrow edema (BME) measurements with radiographic severity and relative cytokine mRNA expression in blood cells.

METHODS: 60 OA patients (mean age 61.45 $\pm$ 10.3, mean BMI 27.5 $\pm$ 3) fulfilling ACR criteria for knee OA were recruited as part of an NIH OA Biomarkers Network-funded project. Standardized semi-flexed radiographs were scored for overall Kellgren and Lawrence (KL) grade, osteophytes, joint space width (JSW) and subchondral sclerosis by the same radiologist. Dynamic 3T MRI was performed before and after contrast agent Gd-DTPA 0.2mg/kg (double dose). . The cartilage volume was quantitated using T1-weighted 3D-flash sequence with water excitation, FOV=15x15 cm, Matrix=512x384, slice thickness=1.5mm, receiver bandwidth=200Hz/pixel, TR/TE=25ms/4ms, Flip angle=25, in the sagittal plane. SV was evaluated with slice thickness=5mm, receiver bandwidth=200Hz/pixel, TR/TE=12ms//3.9ms TE, Flip angle=60, in the sagittal plane. Compartment-wise BME volume was quantified with T2-weighted fat saturated images and in/out of phase images respectively. Peripheral blood mononuclear cells were isolated using Ficoll gradient and total RNA was isolated using Trizol and purified using Qiagen column. The relative gene expressions of selected cytokines (IL-1 and TNF) were quantitated using TaqMan PCR and normalized against GAPDH using 2delta Ct method.

RESULTS: Early OA based on KL score (KL1 and 2) did not correlate with loss of cartilage volume (femoral, patellar and tibial regions) on MRI, but advanced OA by KL scores of 3 and 4 (seen in 50% of our patients) did correlate with increased loss of cartilage volume in the tibial compartment (nearing significance $p<0.08$). However, JSW ($r=0.072$, $p>0.09$) or osteophyte scores ($r=0.03$, $p>0.58$) alone did not correlate with MRI cartilage wear. As internal validation, we also observed significant correlation of increasing subchondral sclerosis ($r=0.61$, $p<0.0001$), osteophyte scores (0.64, $p<0.0001$), and decreasing JSW ($r=-0.62$, $p<0.0001$) by radiography with KL score. When shifting focus to synovial volume, which consists mostly of proliferative synovial tissue, we found a consistent association between this volume and increases in KL scores ($r= 0.54$, $p<0.00001$). In addition, increased SV also correlated specifically with higher radiographic osteophyte scores ($r=0.52$, $p<0.000047$) and subchondral sclerosis ($r=0.46$, $p< 0.00004$), and inversely correlated with JSW ($r=-0.35$, $p=0.01$). Similarly, increasing KL scores demonstrated greater BME, although only with significance in the medial tibia ($r=0.24$, $p<0.08$); additionally, BME had a significant association with subchondral sclerosis ($r=0.38$, $p<0.01$) and near significance with osteophyte scores ($r=0.23$, $p=0.1$).Furthermore, SV strongly correlated with total BME volume ($r=0.46$, $p<0.0006$). Increased SV also correlated significantly with TNF□ ($r=0.386$, $p<0.003$) expression but not with IL-1□from peripheral blood leukocytes (PBL).

CONCLUSIONS: Our data indicate that synovial disease and BME, as reported by MRI, are characteristic features of progressive OA which correlate with osteophyte formation, subchondral sclerosis, joint space narrowing and KL score. In contrast, loss of cartilage volume by MRI is not similarly predictive. Early screening for synovial changes by MRI and cytokine TNFα expression in PBLs could identify patients at risk for progressive disease.

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MRI BASED MORPHOLOGIC GRADING SYSTEM FOR EARLY HIP OSTEOARTHRITIS

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PURPOSE: The aim of this study is to develop a MRI grading system for hip osteoarthritis (OA) based on morphologic changes in cartilage, labrum, and bone.

METHODS: We devised a MRI grading system for early hip OA with standard definitions of morphologic changes with corresponding pictorial atlas. 50 MR images were obtained from 25 patients with hip dysplasia and 25 patients with femoroacetabular impingement. Images were acquired on a Siemens Avanto 1.5T scanner. Trufisp imaging with FoV 140mm, matrix size 384, slice thickness 0.6mm were used for morphologic grading. Three-dimensional dGEMRIC scan was obtained using two angle fast T1 mapping sequence. Additionally, standard pelvic radiographs and WOMAC outcome scores were obtained. The trufisp images were reconstructed in 6 radial projections rotating around the femoral neck axis. These radial images were scored for bone and soft tissue lesions at 7 different positions encompassing most of the articular surface and avoiding the acetabular fossa. A sum score of all lesions seen in the joint was calculated. The sum score (OA score) ranges from 0 to 197 with higher score indicating more OA. We looked at correlations between OA score, Tönnis grade, joint space width (JSW), dGEMRIC index, and WOMAC pain using Spearman rank correlation.
Fig1 shows an example of hip with no radiograph OA (fig1a). On MRI, cartilage damage and bone changes were seen (fig1b).

RESULTS: Mean age of the patients was 29 years. The OA score ranged from 20 to 87 with mean value of 43. Significant correlation was found between OA score and Tönnis grade (r_s=0.39, p=0.006), dGEMRIC index (r_s=-0.35, p=0.01), and WOMAC pain score (r_s=0.48, p=0.001) (fig2). No correlation was found between OA score and JSW.

CONCLUSIONS: In this preliminary result, we attempted to score the bony and soft tissue morphologic changes that occur in early hip OA. We have found good correlation with clinical outcome measure and dGEMRIC index suggesting that this measure is potentially a clinically relevant measure. We are currently attempting to look at the reproducibility of this grading system as well as the local correlation between morphologic changes and local dGEMRIC index.

COMPARISON OF X-RAY AND MRI IN THE DETERMINATION OF OA PROGRESSION IN THE KNEE MEASURED AT A FIXED LOAD-BEARING POSITION IN THE MEDIAL COMPARTMENT

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INTRODUCTION: Radiographic minimum Joint Space Width (minJSW) is the primary structural endpoint used as an indirect measure of articular cartilage thickness in clinical trials of knee OA. Articular cartilage thickness can now be measured directly from MR images. In this study we compare the abilities of the results of JSW and cartilage thickness to measure progression and identify rapid progressors in a subset of the OAI progression group

OBJECTIVE: To determine whether x-ray and MRI measurements made at a common central location in the medial compartment: 1) record similar rates of progression, and 2) correlate in their ranking of subjects according to amount of disease progression.

METHODS: A group of 88 individuals were 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, and evidence of medial osteophytes. KneeAnalyzer software (Optasia Medical, Manchester, UK) was used to make semi-automated annotations of the radiographs. JSW was automatically calculated along a parameterised line bisecting the medial compartment, with its origin (x=0) at the tip of the tibial spine and end (x=1) at the outer medial edge of the joint. The central JSW (cJSW) was measured at x=0.5 on this line. Calibration was made by automated location of Synaflexer beads within the image. Pairs of MR images were manually segmented using EndPoint software (Imorphics, Manchester, UK), using trained segmenters blinded as to time point, but not subject. A dense set of anatomically corresponded points was automatically identified on the femur and tibia bone surfaces, using a 3D appearance model, allowing measurements to be taken at corresponding anatomical locations on each image. Average thickness (ThCtAB) of the cartilage situated inside the meniscal window of the medial femur (wcMF) and the medial tibia (wMT) was calculated. The values for wcMF and wMT were added together to provide a measure of the average thickness of articular cartilage in the meniscal window (MF + MT).

RESULTS: The average change in cJSW using the x-ray method was -0.25mm, or -5.01% (SRM -0.46; and p-value 0.00006). The MRI method showed an average change for (MF + MT) of -0.1mm, or -2.78% (SRM -0.39, p-value 0.00048). However, the correlation between the two measures was poor (R^2 = 0.7412). A Bland Altman plot showed that there was an average bias of 1.35mm between the measures. 95% limits of agreement between the measures were 0.0588 to 2.651 (SD of 0.061). No correlation could be discerned when plotting the amounts of change measured for each subject by the two methods

CONCLUSION: Both methods were able to show progression within this group, with good statistical significance. However, the methods identified different populations of ‘rapid progressors’. Unlike MRI, which measures only the cartilage thickness, X-ray measurement of joint width is taken weight bearing, and will include other factors such as synovial fluid and the behavior of the menisci under load. It is unclear whether the two approaches quantify the same progression in pathology but with poor agreement, or are sensitive to different manifestations of the disease.

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DEVELOPMENT OF AN IMAGE-BASED METHOD TO QUANTIFY CONTACT ARE IN THE ULNOHUMERAL JOINT

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INTRODUCTION: Osteoarthritis is a common sequela of fractures and ligamentous injuries to the joints of the elbow. It is thought that altered articular contact results in overloading of cartilage, predisposing the joint to development of arthritis. Recently, computed tomography and magnetic resonance imaging based approaches have been developed to non-invasively quantify the osseous interactions and contact that occur in joints. To date, these techniques have been employed to a limited extent and often rely on assumptions about cartilage thickness and deformation that have not been validated.

OBJECTIVE: The specific aim of our research was to develop a technique to determine contact patterns at the ulnohumeral joint as a function of elbow flexion using a standardized validated approach.

METHODS: Our technique employs volumetric images generated by computed tomography (CT). Three dimensional (3D) reconstructions of the joint are used to create proximity maps using custom written software in the Visualization Toolkit (VTK). The proximity maps represent the inter-bone distances between articulating surfaces. Joint contact area was defined as the cortical surface area of one bone that is a prescribed threshold distance from the cortical surface of the other bone. A single fresh-frozen cadaveric specimen was chosen showing minimal signs of osteoarthritis for testing purposes. The specimen was sectioned mid-humerus with the tendons of relevant muscles sutured for loading purposes. CT images were acquired with the arm positioned in 90 degrees of flexion and full extension using a CT compatible flexion testing device.

RESULTS: Results indicated a bicentric distribution of contact on the proximal ulna with a ventral and dorsal maxima separated by a non-contacting region. In full extension, the majority of humeral contact occurred on the posterior aspect of the trochlea. Throughout both angles of simulated elbow flexion, the majority of contact occurred on the medial side of the greater sigmoid notch on the proximal ulna and on the medial aspect of the trochlea.

CONCLUSION: Our findings are consistent with current literature on ulnohumeral contact. It is likely that this work will launch an exciting new approach -the non-invasive measurement of joint contact- to more fully elucidate the effects of injuries, medical management and surgical interventions at the elbow.

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THE PUBLIC HEALTH IMPLICATIONSOF DEFINING EARLY OSTEOARTHRITIS: THE TIP OF THE ICEBERG

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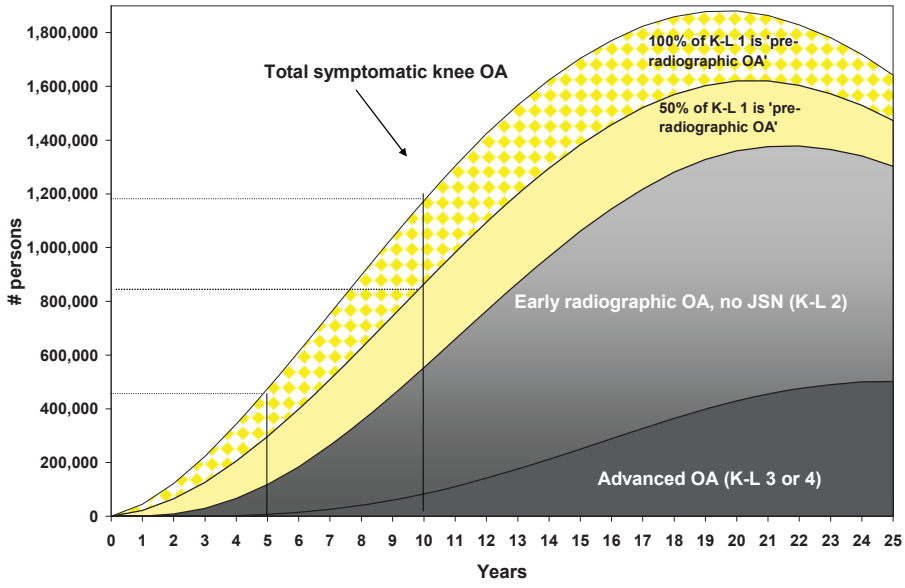
INTRODUCTION: Defining OA based on sophisticated imaging methods will assist in identifying candidates with early, pre-radiographic OA for pharmacologic treatment. However, it will also increase the total number of persons diagnosable with osteoarthritis, with implications for projected disease specific costs and disability. Our objective was to forecast the number of new OA cases diagnosed among radiographic OA–free, asymptomatic persons aged 55-64 years in the US.

METHODS: We used NHANES III data to estimate the number of persons 60-64 years of age who were OA-free (K-L 0, no knee pain), stratified by obesity (cut-off BMI=30). The total population of persons 55-64 years of age was obtained from US Census (2000) data. Annualized incidence and progression of symptomatic OA were derived from the Johnston County (JoCo) OA Project and calibrated to published literature. Mortality was derived from US life tables. The number of persons with any new diagnosable knee OA over the next 25 years was estimated using the Osteoarthritis Policy Model (OAPol), a comprehensive computer simulation model of the natural history and clinical management of knee OA. OA cases were further stratified by severity of disease: early radiographic OA (K-L 2) and advanced OA (K-L 3, 4). Assuming that some K-L 1 patients have cartilage degeneration detectable by more sophisticated imaging modalities such as MRI, we designated 50% of patients with K-L 1 as 'pre-radiographic OA' in the base case analysis. In sensitivity analyses we varied that proportion from 0-100%.

RESULTS: Among 12,995,054 OA-free persons with mean age 60, 117,781 will develop definite (K-L>1) radiographic OA within 5 years. Assuming 50% of persons with knee pain with K-L 1 have 'pre-radiographic OA, the number of incident cases will be increased 2.5 times, up to 295,875. Assuming 100% of persons with K-L 1 have pre-radiographic OA, the number of incident cases will reach 473,969. At 10 years, among those who survive, the number of persons with definitive OA (K-L 2, 3, 4) will reach 552,929, with 82,913 of having advanced OA. Adding 50% of persons with K-L 1 to the pool of knee OA patients will bring the number of new OA cases to 864,204. Including all symptomatic K-L1 persons will double the number of new symptomatic OA cases to 1,175,478.



CONCLUSIONS: A substantial number of OA-free persons will develop knee OA over time. Half of new cases over the next decade will have early OA, detectable by MRI but not by plain radiograph. If substantial number of these cases are diagnosed, the health care system will be further stressed with the additional costs of OA management. Using separate criteria for defining OA and for monitoring OA progression may help to prevent this burden.

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QUANTITATIVE MR IMAGING OF CARTILAGE MORPHOLOGY IN THE PRESENCE OF GD-DTPA IS LESS SENSITIVE TO LONGITUDINAL CHANGE IN OA

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INTRODUCTION: Compositional (proteoglycan) cartilage imaging using delayed gadolinium enhanced MRI (dGEMERIC) needs to be performed 90 mins after intravenous injection of the contrast agend Gd-DTPA. However, the longitudinal sensitivity to change in measurement of cartilage morphology (volume, thickness) has not been compared in presence and absence of Gd-DTPA.

OBJECTIVE: To clarify whether dGEMRIC and morphological cartilage MR imaging must be performed in two sessions (before and 90 mins after Gd-DTPA injection) or whether they can both be performed at a single time point after Gd-DTPA injection.

METHODS: The subsample studied was drawn from 180 female participants (age > 40 years, both with and without OA), recruited at 7 clinical centers (Pfizer 9001140 study). 41 participants completed the baseline and 24 months follow-up MR imaging, both before and after intravenous Gd-DTPA injection. All participants displayed K-L grade 2 or 3 in either the anterior posterior or the Lyon Schuss radiographs acquired at baseline. 1.0mm coronal FLASHwe MR images were acquired with 3.0T Trio (Siemens) and Signa Excite/Genesis Signa (GE) MRI scanners, before and 120 mins after intravenous Gd-DTPA injection. 7 experienced readers segmented the medial (MT) and lateral tibial (LT) and medial (cMF) and lateral weight-bearing femoral condylar (cLF) cartilage, with blinding to the order of acquisition. All segmentations were quality controlled by two readers (F.E. and S.M.). Cartilage volume (VC) and the mean cartilage thickness over the entire subchondral bone area (ThCtAB) were computed using proprietary software. ThCtAB was determined in 5 subregions of the medial and lateral tibia, and in 3 subregions of the weight bearing medial and lateral femur, respectively. The mean change (MC%), SD of change, standardized response mean (SRM = MC/SD) of ThCtAB were calculated in these regions, both for the pre- and post GdDTPA image pairs.

RESULTS: In the absence of Gd-DTPA a 1.7% reduction in cartilage thickness (ThCtAB) was observed over 24 months in the medial tibia (SRM -0.35; $p<0.05$) and a 0.1% reduction (SRM= -0.02; $p=0.92$) in the presence of Gd-DTPA. In the lateral tibia, changes were -2.0 % (SRM= -0.56; $p<0.01$) without and -1.4 % (SRM= -0.32; $p<0.05$) with Gd-DTPA. In the weight bearing medial femur there was a 1.6% decrease in cartilage thickness (SRM -0.20; $p=0.22$) in the pre Gd-DTPA scans, and no significant changes in the post Gd-DTPA images (-0.6% MC, SRM -0.09, $p=0.58$). In the weight-bearing lateral femur however, a significant ($p<0.05$) decrease in ThCtAB (-1.8% MC, SRM -0.34) was observed in the post Gd-DTPA scans; but no significant change in the pre-Gd-DTPA scans (0.9% MC, SRM 0.22, $p=0.16$).

CONCLUSION: Although the differences (in change) were not significant for pre- and post-Gd morphometry, the pre-Gd-DTPA image pairs tended to show greater change and higher SRMs than the post-Gd-DTPA images in the medial femoro-tibial compartment. Because the participants were selected for medial radiographic changes at baseline, cartilage loss was expected in the medial rather than lateral compartment. These results indicate that the sensitivity to change of cartilage morphometry in OA may be diminished by the presence of Gd-DTPA. Further testing will therefore be required, before morphological measurements are made on post-Gd images in longitudinal studies.

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EFFECT OF PATELLAR BRACE ON THREE-DIMENSIONAL PATELLAR TRACKING IN SUBJECTS WITH PATELLOFEMORAL OSTEOARTHRITIS

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INTRODUCTION: Patellar bracing is a common treatment strategy for patellofemoral osteoarthritis (OA); however it is not clear how bracing affects patellar tracking in this population.

OBJECTIVE: The aim of this study was to assess the effect of a patellar brace on three-dimensional patellar tracking (kinematics) in subjects with patellofemoral OA.

METHOD: We assessed three-dimensional patellar kinematics in 10 subjects (7 female, 3 male, 60.9 ± 11.3 yrs, 89.5 ± 19.3 kg) with symptomatic radiographic patellofemoral OA using a validated, quasi-static, MRI-based method. All subjects had radiographic lateral patellofemoral OA and seven had concomitant tibiofemoral OA (KL grade ≥ 2). To assess patellar kinematics, a bone model was created from a T1-weighted MRI (in-plane resolution 0.625 mm). Next, 6 bone outlines were created from 6 quick, static T1-weighted MRIs (in-plane resolution 1.25mm), acquired through a range of approximately 35º of loaded knee flexion. The outlines were registered to the bone models using an iterative closest points algorithm and patellar kinetmatics (flexion, spin and tilt; proximal, lateral and anterior translation) were assessed using custom software (Matlab, the Mathworks, Natick, MA). Each subject underwent 4 assessments of patellar kinematics: 1) no knee brace, no load, 2) no knee brace, 15% bodyweight (BW) load, 3) knee brace, no load, 4) knee brace, 15% BW load. A standard patellofemoral brace was used for all subjects. Splines were fit to each subject's data using the spcvr function in Matlab. Comparisons were made at 1º increments over the coincidental range of knee flexion between the no-brace and brace conditions, at no load and 15% BW load, using a paired t-test with Bonferroni correction for multiple comparisons ($p<0.0042$).

RESULTS: Under no applied load, the brace extended and medially tilted the patellae and shifted them distally, medially and posteriorly (Table 1). There was no difference in patellar spin between the no-brace and brace condition when no load was applied. Under 15% BW load, the brace extended and externally rotated the patellae and shifted them distally, medially and posteriorly (Table 1). There was no difference in patellar tilt between the no-brace and brace condition when the 15% BW load was applied.

	Mean Difference		t-Value		P-Value		95% Lower		95% Upper	
Parameter	no load	15%BW	no load	15%BW	no load	15%BW	no load	15%BW	no load	15%BW
Flexion	2.7	2.4	21.90	14.83	<0.0001	<0.0001	2.4	2.1	2.9	2.8
Spin	0.1	0.3	1.994	3.20	0.0469	0.011	0	0.1	0.2	0.5
Tilt	-1.4	-0.2	-14.856	-0.943	<0.0001	0.3462	-1.6	-0.5	-1.2	0.2
Proximal	0.8	1.3	9.797	16.568	<0.0001	<0.0001	0.6	1.1	0.9	1.4
Lateral	0.5	0.8	14.850	17.841	<0.0001	<0.0001	0.5	0.7	0.6	0.9
Anterior	0.6	0.6	19.945	12.603	<0.0001	<0.0001	0.5	0.5	0.6	0.7

Table 1: Paired t-test for the six kinematic parameters under no load and 15% BW for the no-brace and brace conditions.

CONCLUSION: The largest effect of the brace was to produce more extended patellae in both no load and 15% BW load conditions, which suggests that the brace restricts the patella in flexion/extension. The more distal patellar position with the brace at 15% BW load could also be due to the restriction of proximal/distal patellar motion. Differences in patellar tilt were seen when no load was applied, but not when 15% BW load was applied, which may suggest that the active quadriceps muscle stabilizes patellar tilt in the loaded case. While the effect of bracing on kinematics may appear small, small differences in kinematics have been observed between normals and patients with patellofemoral syndrome, which suggests that braces may produce clinically significant changes in patellar kinematics in subjects with OA.

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REPRODUCIBILITY OF dGEMRIC IN THE HUMAN KNEE JOINT AT 1.5 T

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INTRODUCTION: The delayed gadolinium enhanced MRI of cartilage (dGEMRIC) has been widely used as a biomarker for the proteoglycan content of cartilage, however, information on the reproducibility of the technique is very limited.

OBJECTIVE: To determine the short-term reproducibility of dGEMRIC at different joint surfaces in asymptomatic volunteers at 1.5 Tesla.

METHODS: Ten physically active asymptomatic volunteers (5 female, 5 male) with a mean age of 31.7±6.4 (range 25-47) years and body mass index of 25.3±3.5 (range 22-34) kg/m^2 were recruited. The volunteers had no history of knee injury or surgery and no knee-related symptoms. The dGEMRIC experiment was repeated three times with an average interval of 5±3 five days between scans. The flexion angle and rotation of the knee was controlled by stabilizing the leg to a fixed position with a leg holder and a custom-made inflatable cushion. Intravenous administration of 0.2mM/kg of Gd-DTPA^{2-} (Magnevist, Schering, Berlin) was followed by a 5 minutes of flexion-extension excercises and 5 minutes of walking. After 90 minutes from injection T1-mapping was performed from a single sagittal slice through the center of the lateral femoral condyle and from the center of the patella in the axial plane using an 2-D IR-FSE sequence (TR=1800ms, TE=13ms, TI=1600, 800, 400, 200, 100 and 50 ms, ETL=5, 3-mm slice thickness and 0.36×0.36mm in-plane resolution). Cartilage was manually segmented into (i) a bulk ROI covering all cartilage of each joint surface in the slice, (ii) full thickness ROIs for various segments of the femur (6 segments), tibia (3 segments) and patella (2 segments), and (iii) for superficial and deep halves of cartilage in each segment. The absolute reproducibility, as measured by root-mean-square (RMS) coefficient of variation (CV_{RMS}), and the relative reproducibility, as determined by intraclass correlation coefficient (ICC), was evaluated for each ROI.

RESULTS: The reproducibility for bulk dGEMRIC was 4.2% (ICC: 0.95) for femur, 5.5% (0.87) for tibia and 4.8% (0.97) for patellar cartilage. The reproducibility of full thickness ROIs ranged between 4.8-11.6% (ICC: 0.62-0.98) among different cartilage segments of the femur, tibia and patella. The reproducibility of superficial and deep cartilage ROIs at various topographical locations ranged between 5.2-12.9% (ICC: 0.45-0.93) for femur, 5.8-9.3% (0.45-0.91) for tibia and 4.7-8.3% (0.94-0.98) for patella. The average reproducibility was 5% for bulk ROIs covering all the visible cartilage at each cartilage surface, 7% for full-thickness ROIs, 7% for superficial ROIs and 8% for deep ROIs. Among all ROIs, 33/36 ROIs showed a CV_{RMS} less than 10%.

CONCLUSION: The present results demonstrate mostly good short-term reproducibility for dGEMRIC. Significant variation, however, was observed between topographical locations. The poorest reproducibility was observed for the most posterior part of the femoral condyle which is probably most susceptible to inaccuracies in joint rotation. The highest reproducibility was reported for the patella, which is relatively immune to rotation inaccuracies in the axial plane, has minimal in-plane curvature at the location of the imaged slice and has the largest ROIs. Previously, dGEMRIC has been reported reproducible within 10-15% in a limited number of subjects with up to two months interval between scans (Burstein et al. Magn Reson Med 2001). With the aid of a leg holder and systematic positioning approach reproducibility is likely to improve. Reproducibility has to be separately assessed for three-dimensional sequences.

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Radiographic Features of Osteoarthritis Are Strongly Associated with Knee Pain: The Issue is Settled

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Background: In prior studies, the association between presence or severity of knee pain and radiographic features of OA has been weak to modest, with the only feature tied to pain being osteophytes (OST). However, interindividual differences in pain sensitivity, perception, and tolerance exist due to a variety of factors (e.g. genetic predisposition, prior experience, external influences) and these factors confound prior studies that have examined this question across individuals. One way to eliminate the influence of such factors is to examine the association of radiographic OA with knee pain within individuals who have one knee with pain while the other does not. **Methods**: The Multicenter Osteoarthritis (MOST) Study is a longitudinal observational study of individuals who have or are at high risk for knee OA. Baseline assessment included PA and lateral x-rays. Subjects were asked a question about frequent knee pain (FKP) (pain on most of the past 30 days) and completed the WOMAC. We identified individuals who had knees discordant for the presence of FKP and severity of knee pain (WOMAC score differed between the knees by ≥20% and absolute ≥2). Two such knees within an individual formed a matched set for this analysis. We used conditional logistic regression to evaluate the association of K/L grade, and maximal OST grade and joint-space narrowing (JSN) grade (mutually adjusted), respectively, with these pain outcomes. **Results**: The following # of persons had knees that were discordant for each pain definition: 699 for presence of FKP and 1110 for presence of greater WOMAC pain severity in one knee *vs.* the other. K/L grade, OST grade, and JSN grade (mutually adjusted) were strongly associated with FKP and severity of knee pain (Table). Similar results were obtained with consistency of knee pain. **Conclusions**: Contrary to prior studies, K/L grade was strongly associated with presence and severity of knee pain, even at K/L grades 1 and 2, and JSN was more strongly associated with pain than OST. Thus, radiographic severity as determined by K/L grades and individual radiographic features are good predictors of knee pain presence and severity, and do accurately reflect presence of painful pathology.

Table. Within-Person Matched Knee Analysis: Associations of Frequent Knee Pain and Severity of Knee Pain with K/L grade, Maximal OST, and Maximal JSN grade, respectively, within individuals with knees discordant for pain status. OR (95% CI)

Radiographic Feature	Freq Knee Pain *vs.* No Pain (n=699 persons)	Greater *vs.* Lesser Pain Severity (based on WOMAC difference ≥20% and absolute ≥2) (n=1110 persons)
K/L Grade		
K/L=0	1.0 (ref)	1.0 (ref)
K/L=1	1.5 (0.9-2.3)	1.50 (1.04-2.16)
K/L=2	3.9 (2.4-6.5)	3.77 (2.51-5.69)
K/L=3	9.0 (5.2-15.6)	9.03 (5.76-4.15)
K/L=4	150.7 (43.1-526.4)	54.06 (26.42-110.60)
P for trend	P<0.0001	P<0.0001
Max OST & Max JSN (mutually adjusted for one another)		
OST=0	1.0 (ref)	1.0 (ref)
OST=1	1.2 (0.8-1.8)	1.27 (0.89-1.82)
OST=2	2.0 (1.1-3.7)	2.71 (1.63-4.49)
OST=3	2.0 (1.0-4.2)	2.51 (1.38-4.57)
P for trend	P=0.07	P=0.001
JSN=0	1.0 (ref)	1.0 (ref)
JSN=1	2.4 (1.5-3.8)	1.94 (1.33-2.83)
JSN=2	5.4 (2.9-10.0)	4.17 (2.54-6.84)
JSN=3	96.7 (26.4-353.9)	24.84 (11.66-52.88)
P for trend	P<0.0001	P<0.0001

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FOLATE MEDIATED IMAGING OF ACTIVATED MACROPHAGES IN EXPERIMENTAL OSTEOARTHRITIS USING SPECT/CT

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INTRODUCTION: Macrophages might play an important role in the development of OA for they can produce a large variety of enzymes and pro-inflammatory cytokines. These mediators are known to have pathogenic and destructive effects on all joint tissues. Thus evaluation of macrophage action may provide essential information about etiology as well as progression rate of osteoarthritis. Once active, macrophages abundantly express the functional form of the folate-receptor-β (FR-β), which binds the vitamin folic acid with high affinity. By targeting the FR-β using radioactive labeled folic acid, one can image macrophage activity *in-vivo* in *real*-time.

OBJECTIVE: Imaging macrophage activity and involvement in experimental osteoarthritis

METHODS: Animal models: experimental OA was induced in male Wistar rats by intra-articular injection of 3 mg mono-iodoacetate (MIA) into the knee (biochemical model, n=4); transection of the anterior cruciate ligament (ACLT, surgical model, n=2). An experimental rheumatoid arthritis (RA) model, (mBSA-model) in which activated macrophages are known to be involved abundantly, was used as a positive control condition (n=2). 24 hours prior to imaging the animals we injected with radioactive labeled folic acid (111In-DOTA-FA). Images of the animals were obtained using a dedicated small animal multipinhole SPECT/CT camera (nano-SPECT/CT, Bioscan inc.) at 3, 9, 15, 27, 41 and 52 days after OA induction. (Specifications of the *in-vivo* scans : SPECT:±500µm res. , µCT: ±200µm res. total: 30 min. acquisition time).

RESULTS: All three models (RA, ACLT, MIA) showed increased uptake of the 111In-DOTA-FA, not only in the synovial region of the knee, but also in the plopliteal and inguinal lymph node regions. However, the uptake of activity was less in the experimental OA models than in the RA model. The MIA model showed a higher activity rate in the lymph node regions than was seen in the ACLT-model.

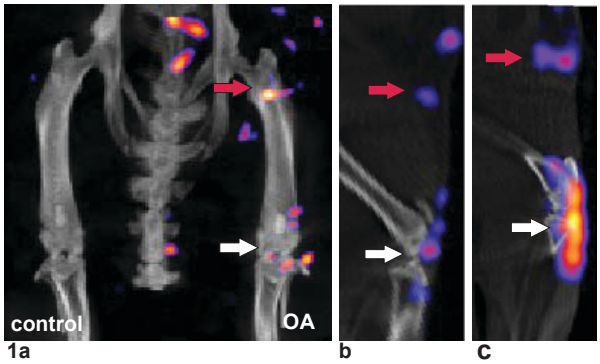

Fig. 1a, b, c SPECT/CT image of rats 24 days after MIA injection a, b; and aclt treatment c. Fig.1a is a 3D projection, b and c are images of OA knees in the saggital plane Note the synovial activation (white arrows and lymph-node activation (red arrows). (SPECT in color, CT in grey)

CONCLUSION: Macrophage activation in experimental OA could clearly be monitored by SPECT/CT in combination with a folate tracer. As expected we found increased activation around the knee area, probably the synovium, though the amount of activity of macrophages in the lymphoid system up to the inguinal nodes in experimental OA was not as expected. This shows that macrophages play not only a local role but are also involved in a more systemic response to the affected knee. This response is known in RA, in which macrophages have a (auto-)antigen presenting role in the lymph-nodes. Though, such a role for OA is not known. By investigating a surgical as well as a biochemical OA-model it becomes less likely that there is a direct response of macrophages to the specific models, as lymph-node activation was high in both models till the end of the experiment (7.5wks). To conclude, *in-vivo* visualization of activated macrophages in OA provides more insight in OA etiology and enables to monitor OA intervention strategies.

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DELAYED GADOLINIUM ENHANCED MRI OF CARTILAGE (dGEMRIC) AFTER ACL TEAR

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INTRODUCTION: Early detection of changes in articular cartilage may provide insight into the mechanisms of cartilage degeneration in this high-risk patient population. Delayed Gadolinium-Enhanced MR Imaging of Cartilage (dGEMRIC) is an imaging technique that creates T1-maps of hyaline cartilage following the intravenous administration of $Gd(DTPA)_2$ contrast to infer glycosaminoglycan (GAG) concentration in articular cartilage (Burstein 2003). Since hyaline cartilage matrix is composed of GAG molecules with negatively-charged carboxyl and sulfate groups they will repel negatively charged $Gd(DTPA)_2$ ions. As a result, $Gd(DTPA)_2$ concentration will be higher in regions with low GAG concentration, which produces a reduction in the measured T1-relaxation time of cartilage. It is also known that the T1 relaxation time is affected by duration between contrast agent administration and imaging, thus a separate control group is generally employed for these kinds of studies (Tiderius 2005).

OBJECTIVE: 1) To compare femoral and tibial articular cartilage in the injured and non-injured knee after acute ACL tear using the dGEMRIC index as a biomarker of GAG content in articular cartilage. We expected lower dGEMRIC values, signifying lower GAG content, in the injured knee compared to the contralateral uninjured knee. We also wanted to show that both knees could be imaged in one MRI session following one administration of contrast agent.

METHODS: Subjects consisted of five men and seven women (mean age 33 years; range 20-49) who satisfied the following inclusion criteria: unilateral ACL injury, no prior history of knee injury, pathology, or predisposing conditions. The median time between injury and MR imaging was 67.5 days. dGEMRIC was performed on a 1.5T Siemens Symphony magnet using the following protocol: 1) Each subject was administered 0.2 mmol/kg of $Gd(DTPA)_2$ (Magnevist®, Bayer Healthcare) contrast agent, followed by a saline flush. 2) Immediately after injection, each subject walked for 10 minutes to promote diffusion of the contrast agent into synovial fluid and cartilage. 3) At approximately 90 min. post-injection, a series of five fast spin echo inversion recovery sequences (inversion times of 1650ms, 650ms, 350ms, 150ms, and 28ms) in the mid-sagittal plane through the medial femoral condyle was acquired in the injured and uninjured knees. These images provided the data to construct the T1 map of articular cartilage. 4) dGEMRIC was performed in the injured and contralateral uninjured knees sequentially, however, the order was alternated such that the injured knee was scanned first in odd numbered subjects and second in even numbered subjects. This was done to control for potential bias in T1-measurements because of differences in contrast delivery times. The MRImapper software package (2006a R2; Beth Israel Deaconess Medical Center, Boston, MA) was used to create mid-sagittal T1 maps of the femoral and tibial articular cartilage of each knee and to calculate the dGEMRIC index.

RESULTS: The mean (± sd) dGEMRIC indexes of femoral articular cartilage in the injured and uninjured knee are 420 ±37ms and 460 ±49ms (p=.005), respectively. The mean dGEMRIC indexes of tibial articular cartilage in the injured and uninjured knee are 408 ±39ms and 452 ±39ms (p=.006), respectively.

CONCLUSION: dGEMRIC demonstrates a significantly lower GAG content in femoral and tibial articular cartilage in ACL deficient-knees compared to the contralateral, uninjured knees. This result suggests that changes in the composition of articular cartilage, which may lead to OA, may be identified relatively soon after ACL injury. The difference in GAG content between knees was detected in one imaging session despite the ten minute delay in imaging time.

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SEMIQUANTITATIVE ASSESSMENT OF PERIPATELLAR SYNOVITIS IN OSTEOARTHRITIS: A COMPARATIVE STUDY OF NON-ENHANCED VS. CONTRAST-ENHANCED MRI

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INTRODUCTION: MRI studies of synovitis in relation to rheumatoid arthritis and osteoarthritis (OA) demonstrate that quantification of synovitis is ideally performed on contrast-enhanced (CE) T1-weighted (T1w) sequences. However, as contrast application is costly, invasive and has potential side effects CE MRI has not been widely applied in large epidemiological studies. To date, semiquantitative (SQ) assessment of synovitis in large studies of OA is usually performed on non-enhanced T2-weighted or proton-density weighted fat-suppressed (PDFS) images. Commonly, signal changes (areas of high signal intensity) in Hoffa's fat pad (HFP) in the infrapatellar and intercondylar regions are scored as surrogates for synovitis. However, radiological differential diagnoses of signal changes in HFP could lead to overestimation of synovitis on non-enhanced scans. It is not known if these signal changes correlate well with the synovitic expressions seen on T1w scans after contrast application.

OBJECTIVE: Aims of the study were 1) to evaluate agreement between signal changes in HFP scored on non-enhanced and enhanced sequences, 2) to assess the diagnostic performance of signal changes detected in HFP on non-enhanced sequences with a reference standard of contrast enhancement in the same location and 3) to examine whether the described signal changes in HFP on enhanced and non-enhanced scans correlate with peripatellar synovial thickening assessed on T1w FS CE sequences.

METHODS: 50 consecutive patients (62% women, mean age 65.2 ± 9.37 years) with OA of the knee were included. 1.5T MRI was performed with triplanar PDFS sequences (TR 5,080 ms, TE 32 ms, slice thickness 3.0 mm,) and a sagittal T1w FS CE sequence (TR 720 ms, TE 15 ms, slice thickness 3.0 mm). Signal alterations in HFP were scored semiquantitatively from 0 to 3 in the infrapatellar and intercondylar regions on non-enhanced and CE images by two radiologists (FWR, AG) in consensus. Peripatellar synovial thickness was measured in the T1w FS CE images in 6 locations and also scored from 0 to 3. Thickness scores were summed and subdivided into 3 grades of summed thickness: grade 1=summed scores of 0-6; grade 2=summed scores of 7-12; grade 3=summed scores of 13-18. Agreement between signal changes scored on non-enhanced and CE sequences was assessed using kappa statistics. Sensitivity, specificity and accuracy were calculated with the T1w CE sequence as the reference standard. In addition we also examined the relationship between signal changes and summed synovial thickness using Spearman's rank correlation coefficient.

RESULTS: Agreement between signal changes on non-enhanced vs. CE MRI was fair to moderate (w-κ 0.35 and 0.45). Sensitivity of signal changes in HFP on PDFS images was high (86% to 100%), but specificity was low (10% to 36%). The main direction of the mis-classification was over-estimation on non-enhanced imaging. A moderate correlation was found between summed thickness scores with infrapatellar (ρ = 0.60) and intercondylar (ρ = 0.53) signal changes, respectively, on the CE images. The correlation for the non-enhanced signal changes and summed thickness scores was low (ρ = 0.34 and 0.29, respectively).

CONCLUSION: Signal changes seen in HFP on non-enhanced images do not always represent synovitis but are a non-specific, albeit sensitive finding. Semiquantitative scoring of peripatellar synovitis in OA ideally should be performed using T1w CE sequences and should include measurements of synovial thickness.

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CONTRAST-ENHANCED MRI OF SUBCHONDRAL CYSTS: THE MOST STUDY

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INTRODUCTION: MRI is sensitive to detect small subchondral cysts, demonstrating well-defined rounded areas of fluid-like signal intensity on non-enhanced imaging. Per definition signal characteristics of cysts show hypointensity on T1w, hyperintensity on T2w images and no contrast enhancement after i.v. application of MR contrast material (gadolinium DTPA). Surprisingly, in a small subset of subjects with or at risk of developing OA we observed contrast enhancement (CE) within subchondral cysts after gadolinium application. It is not known what percentage of subchondral cysts exhibits CE and why this is the case.

OBJECTIVE: 1) To describe the proportion of enhancing SCs as well as contrast-enhancement patterns and 2) to discuss possible radiological explanations of cyst enhancement.

METHODS: The Multicenter Osteoarthritis (MOST) Study is a NIH-funded longitudinal observational study of individuals who have or are at high risk for knee OA. The sample used for the analysis was a cross-sectional subset of the MRI examinations from the 30-month follow-up visit. All subjects with available non-enhanced and CE MRIs were included. The non-enhanced MRI was performed at a 1.0 T extremity system. The MRI protocol included axial and sagittal proton-density weighted fat-suppressed fast spin sequences. Subjects received a 1.5 T MRI after i.v. gadolinium application within 0-30 days after the non-enhanced study (95% on the same day). Axial and sagittal T1w CE sequences were acquired. Two musculoskeletal radiologists read the MRIs (MDC, MDM). The tibiofemoral joint was subdivided into 10 subregions and the patellofemoral joint was subdivided into 4 subregions. Cyst size was scored on the non-enhanced scans semiquantitatively from 0 to 3. Cyst enhancement was scored on the CE sequences as grade 0 (no enhancement), grade 1 (partial enhancement) or 2 (full enhancement). Adjacent cartilage morphology was graded as 0 (intact cartilage), 1 (partial thickness loss) or 2 (full thickness loss). Adjacent bone marrow edema lesion (BML) status was scored as either BML-absent or –present.

RESULTS: 260 subchondral cysts were observed in 400 knees. Concerning size, 222 cysts were grade-1, 36 grade-2 and 4 grade-3 cysts. Of these, 245 (94.2%) showed full CE, 12 (4.6%) showed partial CE and 3 (1.1%) showed no enhancement. In 43.1% of subregions adjacent cartilage was intact or showed partial thickness defects. 91% of enhancing cysts were observed in subregions with concomitant BMLs.

CONCLUSION: Surprisingly, the large majority of subchondral cysts showed contrast enhancement after gadolinium administration. In about half of the cases, adjacent cartilage status did not show full thickness loss. Thus, enhancing synovial intrusion seems unlikely. Most cysts were observed in subregions with concomitant BMLs, which represent areas of increased bone remodeling and perfusion. Diffusion of gadolinium from the subchondral bone into the cysts might explain our findings. The subchondral cysts described did not present with the typical MRI-defined findings of cysts. Subchondral “cyst-like” bone marrow lesion might be a more appropriate term.

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CAN MUSCULOSKELETAL ULTRASOUND CONTRIBUTE SIGNIFICANTLY TO OA RESEARCH ?

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Background / **Forum** Question: Musculoskeletal ultrasound (MSUS) has become a common tool in rheumatology, largely because it is safer, faster, more cost effective and less anxiety-producing than other types of imaging including MRI. While utilized more frequently in the inflammatory arthritides and soft tissue syndromes, many have raised its potential role as a biomarker in OA research. Can we adequately and efficaciously perform MSUS on OA cartilage and possibly other structures (i.e. synovium) to reduce our dependence on resource-draining MRIs ? Is MSUS better in some anatomic locations or for obtaining certain types of radiologic information ?

The Recent Literature The main indications for using MSUS in OA include evaluation of articular cartilage, synovium and adjacent soft tissues, and guidance with injections. But MSUS has also gained interest as a tool for following the structural progression of OA in research studies, and may serve as a biomarker for therapeutic trials.[1] Most efforts have focused on the knee, given its larger acoustic windows and prevalence of disease, but articles on hand OA have emerged with suggested scoring systems[2] and comparisons of MSUS with x-rays[3]; hip OA has received some attention as well.[4-5] While most focus on gray scale and power Doppler, others have introduced contrast-enhanced US[6] and 3D US into the array.

Yet at this time, we still lack an international consensus on how to score articular cartilage, as well as definitions of other common OA findings such as synovial hypertrophy,[7-8] hampering reproducibility and the ability to evaluate studies fairly. Compared to RA, only sparse data exist directly comparing MRI and US evaluation of OA -- thus our pilot data is shown in the section below. There has been relatively little investigation of MSUS in OA published in the last few years, and there was only one such abstract at both the annual ACR and OARSI meetings in 2007. Perhaps the tide may be turning – as the upcoming OARSI meeting in Rome this fall will include a full session on MSUS OA research.

Our Pilot Data: Over the previous year we have started using MSUS to scan the knees of patients in our NIH-funded study of leukocyte gene expression in relation to OA progression predicted by MRI-tracked cartilage degradation. In looking at these patients, and others in some of our multicenter imaging studies, we are actively comparing US evidence of cartilage breakdown, osteophyte formation, and synovitis to the different imaging modalities (x-ray and MRI).

Our preliminary findings center around a cohort of 10 consecutive patients with painful knee OA diagnosed by conventional radiography and gadolinium-enhanced MRI. Our US images of the femoral articular cartilage identified degeneration in 8 of the 10 patients, and corroborated the presence of medial osteophytes in 8 of the 9 patients who demonstrated them on x-ray and MRI. We were less successful in identifying synovitis seen on MRI (4 of 6 patients), in part due to operator inexperience.
We now aim to extend these observations to a larger cohort of patients, and stratify the data by age, gender, KL severity subgroups, alignment, and potentially gene expression profiles. In addition, we plan to ultrasound and x-ray the DIPs and CMCs of our knee OA patients even if their hands are asymptomatic.

Conclusion: A growing literature advocates MSUS as another potentially useful tool in OA imaging research. MSUS could have numerous applications in this field, and may soon serve as a biomarker to gauge response to new treatment options for OA – and in multiple anatomic locations. While it may trump MRI in terms of cost, speed and patient safety, further study is needed to determine if these factors and its dynamic images are sufficient to place MSUS on par with MRI for OA research studies.

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OAI MR QUALITY ASSURANCE METHODS AND RESULTS

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INTRODUCTION: In longitudinal imaging studies standardized Quality Assurance (QA) methods are often used to correct slowly developing problems prior to their impacting image quality or quantitative analysis results. For the OAI, monthly preventative maintenance of the MR systems was performed by the manufacturer and independent QA was systematically performed with standardized phantoms, image acquisitions and analysis methods.

OBJECTIVE: 1) To outline the OAI's MR system QA processes and present the first three years' results. 2) To compare the longitudinal QA variations to test-retest precision and rates of longitudinal change of cartilage morphometry quantification using MR.

METHODS: The four OAI Trio MR systems (Siemens Medical Solutions, Erlangen, Germany) underwent QA acquisitions which were subsequently analyzed by an automated computer program. Key image characteristics such as signal-to-noise (SNR), contrast-to-noise (CNR), signal uniformity, T2 relaxation times, absence of artifacts, gradient calibration, local and global geometric distortion were quantified monthly.

RESULTS: Over a three year period, key criteria for quantitative cartilage morphometry were excellent with a 190.0mm diameter and 148.0mm length object having reproducible diameter (0.04% RMS CV%) and length (0.56% RMS CV%). This resulted in spherical volume reproducibility of 0.46% (RMS CV%). Ghost levels were consistently $\leq$0.2%. T2 relaxation time varied longitudinally site by site from 2.3% to 18.8% RMS CV%. All other measures of MR system stability were met except: 3.0mm and 5.0mm slice thicknesses were consistently larger than expected; knee coil signal uniformity and signal level varied significantly over time.

CONCLUSION: OAI MR QA results compared favorably to prior publications and identified similar technical issues for geometric measurements. The longitudinal variations in geometric distortion should have minimal impact on the accuracy and reproducibility of ThC and VC because spherical volume variations were 5-20 times smaller than the reanalysis (unpaired) error (2.3%-8.5% in 19 participants) and 2-10 times smaller than the paired precision error found in 3T MR knee studies for the weight-bearing femorotibial cartilage plates (2.1%-3.9% in one study of 158 participants and 0.9%-4.8% in another study of 12 participants). This stability should enable direct comparison of baseline and follow-up images and should not significantly contribute to the low annual rates of VC loss (1-3% per year) recently measured by multiple longitudinal studies. Cross-comparison of the results from all four OAI sites reveal that the MR systems are sufficiently uniform to enable results to be combined.

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SEGMENTATION OF KNEE CARTILAGES ON 3.0T MR IMAGES FROM THE OSTEOARTHRITIS INITIATIVE (OAI) WITH A SEMI-AUTOMATED GRAPH-CUTS METHOD AND A MANUAL DELINEATION METHODS

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INTRODUCTION: The pathogenesis of osteoarthritis (OA) is highly associated with cartilage degeneration. Reliable quantification of cartilage morphologies (volume or thickness) from a large database such as OAI requires an efficient and reproducible segmentation method.

OBJECTIVE: To evaluate and compare, between semi-automated graph-cuts and manual delineation methods, the efficiency and reproducibility for the segmentation of knee cartilages on MR images.

METHODS: Nine right knee MR image sets of varying severities of OA [determined by Kellgren-Lawrence (KL) grade] were selected from the sagittal double-echo steady-state (DESS) MR images in OAI-0.B.1 Imaging Data Set (Siemens 3.0T Trio, 160 slices with 0.7 mm thickness) : one set with KL 0; 3 with KL 1; 3 with KL2; and 2 with KL 3. Two radiologist readers (1 and 2) segmented the knee cartilage on 'every third' slice by manual boundary delineation (M method: M1 and M2). Segmentation was repeated using the semi-automated method, which was based on a graph-cuts algorithm (SA method: SA1 and SA2). The SA method incorporates the seeds specified by a reader and intensity values to compute the optimal segmentation. Seed specification and computation were iterated allowing the reader to edit and improve segmentation results. The efficiency in segmentation was measured in terms of segmentation processing time used by readers. The inter-reader reproducibility in segmentation was determined by superimposing the segmented cartilages (M1 onto M2) and (SA1 onto SA2). Then, Dice Similarity Coefficient (DSC; i.e., ratio of overlapped volume/mean volume) was computed as an index for matching between the segmented cartilages. Perfect match corresponds to 100% DSC. In addition, the inter-method reproducibility of a reader was measured by computing DSC's of (SA1 onto M1) and (SA2 onto M2).

RESULTS: The manual segmentation processing time (mean±SD, min) was (160±45) for M1 and (121±27) for M2. On the other hand, the SA processing time, which was based on 'every' slice, was (54±14) for SA1 and (33±6) for SA2, indicating that the SA method was significantly more efficient than the manual method ($p < 0.001$). The inter-reader reproducibility of each method measured by DSC (mean±SD) was 94.2±1.5% (SA1 onto SA2) and 87.7±1.3% (M1 onto M2), indicating that the semi-automated method was significantly higher in inter-reader reproducibility than the manual method ($p < 0.001$). Finally, the inter-method reproducibility of a reader also measured by DSC was 87.4±1.6% (SA1 onto M1) for reader 1 and 87.7±1.2% (SA2 onto M2) for reader 2, which subjectively supports the feasibility of the SA method as an alternative to the manual delineation method.

CONCLUSION: Compared to a manual boundary delineation method, the semi-automated graph-cuts method allowed us to segment knee cartilages with significantly higher (approximately 10 times) efficiency and reproducibility.

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ASSESSMENT OF LOCAL GLYCOSAMINOGLYCAN DISTRIBUTION IN ARTHRITIC HIPS WITH 3-D FAST 2 ANGLE T1 MAPPING TECHNIQUE FOR dGEMRIC

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INTRODUCTION: The use of delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) has been well characterized in various studies, most commonly applied to the knee and hip. Until recently virtually all reported work on dGEMRIC has employed quantitative T1 mapping based on single slice two-dimensional inversion recovery fast spin-echo sequences. The limitations of 2D IR-FSE acquisition are clear: single slice sequences provide limited coverage and IR-FSE sequences require long scan times and are susceptible to motion artifacts. While a 3D Look-Locker acquisition dGEMRIC technique ("Accuracy of T1 Measurement With 3-D Look-Locker Technique for dGEMRIC" published in JMRI. 2008(27)) has been recently reported for use in the knee, the requirement for high resolution coverage of the spherical hip joint led us to implement a 3-D fast 2 angle T1 mapping technique to assess the radial pattern of glycosaminoglycan (GAG) distribution in articular and femoral cartilage of the hip.

PURPOSE: The purpose of the current study was to validate and implement a 3-D isotropic fast T1 mapping sequence for dGEMRIC in order to assess the radial distribution of GAG in the hip among patients with varying degrees of osteoarthritis.

METHODS: Thirty-five hips in 35 patients presenting with radiographic evidence of arthritis in the hip were imaged using a 3D isotropic fast T1 mapping dGEMRIC sequence (TR 15 msec, TE 3.27 msec, flip angles of 4.1 and 23.5 deg., Matrix size 192/192, 16 cm FoV, voxel size 0.8 x 0.8 x 0.8 mm) and a previously validated fast T1 mapping dGEMRIC sequence (voxel size 0.6 x 0.6 x 4 mm) for comparison. Correlation between coronal plane dGEMRIC indices, measured by both sequences, was assessed using Pearson's linear regression. Following sequence validation, 3D image data was reconstructed into 9 radial slices spaced 30 deg. apart and oriented orthogonally to the acetabular opening (excluding the fossa). In each slice, a dGEMRIC index was calculated as the mean T1 of the acetabular and femoral cartilage between the vertical center and peripheral edge of the joint, excluding the labrum. Patterns of dGEMRIC index distribution across the 9 radial positions, anterior to superior to posterior, were compared for hips with varying amounts of arthritis. In 10 patients, the correlation between morphological score (radial segments were classified as normal, visible signal intensity, and severe on standard MRI) and radial dGEMRIC index was assessed using Spearman's linear regression.

RESULTS: 3D fast T1 mapping sequence measurements correlated well to previously validated sequence measurements (Pearson regression coefficient R2 = 0.958). Radial data was stratified by overall dGEMRIC score (mean of 9 radial dGEMRIC indices) into 4 arthritis grades: grade 3 (n = 5, mean = 293 ms), grade 2 (n = 10, mean = 380 ms), grade 1 (n = 10, mean = 488 ms), and grade 0 (n = 10, mean = 597 ms). A consistent pattern was observed in which the highest dGEMRIC index occurring in the superior regions of the joint cartilage in the grade 0-2 hips: mean superior and superior-posterior dGEMRIC indices were significantly greater than overall dGEMRIC scores ($p < 0.05$). In grade 3 hips, an inverted pattern of GAG distribution was observed: superior regions displayed significantly lower dGEMRIC indices in comparison to overall dGEMRIC scores ($p < 0.05$). Spearman's regression analysis revealed a significant correlation between morphological characterization and dGEMRIC index for local radial segments ($p < 0.01$).

CONCLUSION: Using a 3D fast T1 mapping dGEMRIC method to assess the GAG content in local cartilage segments around the acetabulum in vivo, we have reproduced the charge-density distribution reported in previous histological studies. 3D dGEMRIC is a powerful diagnostic tool and combined with morphologic assessments will enable the in vivo characterization of cartilage degradation in early osteoarthritis in future long-term studies.

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3D METHOD FOR THE AUTOMATED ANALYSIS OF THE KNEE JOINT SPACE: MRI DATA FROM THE OSTEOARTHRITIS INITIATIVE

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INTRODUCTION: The quantitative image analysis of high-resolution structural 3D MRI data from the OAI public data sets is challenging due the large number of slices to be analyzed. Robust and automated methods are required to enable the effective evaluation and quantification of the OAI data sets.

OBJECTIVE: To evaluate a fully automated method for the segmentation of the femur, tibia and patella of the human knee joint and evaluate the three dimensional (3D) joint space width as a candidate for the quantitative evaluation of OA related changes.

METHODS: Publicly available registration algorithms from the ITK (http://www.itk.org) were build in a windows vista system and tested for an atlas based segmentation of the right knee of 82 “progression cohort” subjects from the OAI data public use data sets release 0.C.1, 1.C.1 and 2.D.1. First, the femur, tibia and patella, were manually segmented from sagittal 3D MRI DESS images of a normally looking right knee. Then the weight bearing areas, medial tibia-femoral, lateral tibia-femoral and patella-femoral, were defined. The combination of an affine registration algorithm and a spline deformable registration algorithm were used to independently register the femur, the tibia and the patella. The independent registration parameters of the femur, tibia and patella were used to map automatically the segmentation of the normal subject knee into the sagittal MRI DESS series of the three time points (Baseline, 12 months and 18 months). After the mapping, each one of the segmentations was relaxed to maximize the probability of voxel classification into bone or other soft tissues. Once the automated segmentation of the bones was completed, the average distance between bones at joint spaces were computed for each MRI imaging time point and statistically analyzed. The statistical analysis included the correlation of the baseline 3D medial joint space width (3D MJSW) to the total WOMAC scores of the right knee and the correlation of the change in 3D joint space to the baseline total WOMAC right knee scores.

RESULTS: In a period of two weeks 246 time points were analyzed. From the 246 analyzed time points, the registration algorithm successfully registered 245 femurs, 244 tibias and 222 patellas. The success rate of the femur and tibia allowed for the complete longitudinal analysis of the right knee’s medial joint space of 80 subjects. The right knee 3D joint space width of the medial tibia-femoral joint (3DMJSW) showed a week correlation to the baseline WOMAC total right knee scores ($r=-0.27$, $p=0.01$). A positive correlation was observed between BL WOMAC total score at the right knee and the 3DMJSW change between baseline (BL) and 12 Months ($r=0.30$,$p<0.01$). On the other hand, a stronger negative correlation was observed between the BL WOMAC total right knee score and the 3DMJSW change between 12 months and 18 months ($r=-0.38$,$p<0.01$).

CONCLUSION: This pilot study showed that a fully automated analysis of the bones in 3D MR DESS images is possible; further that the analysis of their segmentation provides valuable and measurable OA related information. The preliminary analysis of the 3D joints space shows that 3D MJSW is correlated to clinical symptoms of OA and that the apparent change in the 3D MJSW is also correlated to the WOMAC total scores.
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Age, DJD, OA: AGE, GAG, T1ρ MRI

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INTRODUCTION: Accumulation of advanced glycation endproducts (AGEs) plays an important role in the general aging process, and has been implicated in the etiology of cartilage degeneration in OA. Articular cartilage chondrocytes exhibit decreased proteoglycan and collagen synthesis and water content may decline at increased AGE levels. Pentosidine, one AGE, crosslinks collagen fibers and results in increased stiffness and brittleness of articular cartilage, rendering it more prone to mechanical damage.

OBJECTIVE: This study examines potential AGE effects on PG-sensitive T1ρ MRI maps as they relate to identification of early pre-symptomatic OA.

METHODS: The knee of a 45 year-old male was retrieved at amputation for pelvic cancer and immediately imaged in a 3T Siemens TIM Trio. The scan acquired twelve slices taken every 5mm (3mm thick with 2mm gap), aligned with a plane through the lateral condyle midline, using a proteoglycan (PG) sensitive spin-lock pulse sequence to measure the relaxation constant T1ρ (the spin-lattice relaxation in the rotating frame). When disarticulated, the asymptomatic knee exhibited surface roughness and discoloration consistent with accumulation of AGEs. A transparency template of 5mm squares was aligned with the lateral condyle midline, followed by removal of osteochondral specimens with a 4mm dermal punch; 15 each from the weight-bearing surfaces of the femoral condyles, tibial plateaus, and patella; 21 from the non-weight-bearing femoral trochlea and sulcus cartilage. A follow-up isotropic 3D fat-suppressed VIBE MRI generated volumetric information needed to explicitly locate and register the cartilage biopsy locations in the prior T1ρ images. After MR imaging, the chondral explants were assayed for PG content by dimethylmethylene blue colorimetry. Ten additional articular cartilage samples (2 from each of the 4 weight-bearing regions and 2 from the trochlear notch) were assayed using high performance liquid chromatography (HPLC) for the collagen cross-link AGE pentosidine, with respect to hydroxyproline, a measure of total collagen content.

RESULTS: A sagittal MRI section maps PG-sensitive T1ρ contours from the mid-lateral condyle populated with its assay results (Figure 1). The lateral condyle of a young female, 4 months after ACL reconstruction, shows healing cartilage without the accumulation of AGEs.

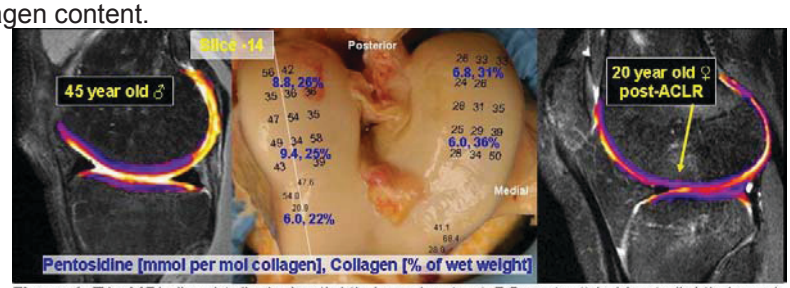

Figure 1. T1ρ MRI slice 14 displaying tightly bound water (↑PG content) in blue to lightly bound water in white (line indicates slice location). DMMB results for PG μg are listed in black. HPCL results for pentosidine and collagen are shown in blue.

CONCLUSION: Pentosidine levels throughout the joint were 3-4 times normal for his age (on average 6.8 mmol/mol collagen). Collagen levels were nearly equally distributed with the highest levels in the lateral condyle. PG content was also greater in the lateral condyle than the medial condyle. Where T1ρ maps of normal articular cartilage show tightly bound water to the subchondral bone, these MRI slices through highly cross-link-aged cartilage exhibit lesser binding of water both below and above the densest PG regions. Direct correlation of PG and T1ρ values on a plug-size scale were not linearly related. These results suggest that inhomogeneous changes in T1ρ maps of articular cartilage may be an indicator of early joint degeneration, and in tandem with related biomarkers may indicate early OA development.

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BONE/CARTILAGE INTERFACE EVENTS IN OA - DO THEY MATTER?

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Although cartilage degradation and loss has been an established indicator of osteoarthritic progression, other changes to the underlying bone may precede gross cartilage changes and provide an earlier indication of deteriorating joint health. The changes in the bone /cartilage interface, including shape (deformation, flattening) and structure (surface, micro crack formation) have been documented in the literature for decades. Why have they not been associated with OA progression? One answer is that tools for objectively measuring and quantifying the bone/cartilage interface changes have not been available until very recently, and are still painstakingly laborious to apply. This paper presents a summary of the bone/cartilage interface changes that have been documented in the literature as a basis for applied research using new image analysis technology to better understand how these changes are associated to each other and to the changes in joint health.

What is the bone cartilage interface histologically and in images?

There are three calcified components in the joint; subchondral trabecular bone, subchondral bone plate and calcified cartilage. Subchondral bone plate is woven bone, which separates the trabecular bone from the calcified cartilage. Calcified cartilage is separated by the tide mark from non calcified cartilage. Histologically, the bone cartilage interface is between the calcified cartilage and the subchondral bone plate. The trabecular bone and subchondral bone plate are well seen in all imaging modalities. However, the tide mark, not the subchondral bone plate, forms the visual outer border of the articulating bone surfaces. That is the smooth surface we see in plain films, MRI and CT. Thus, every event that affects the tidemark should also be seen in images.

The events affecting the tidemark during the growth period and after growth period

During the growth period the bone grows in length and width through enchondral ossification. In this process the tidemark and the calcified cartilage advance toward the articulating surface of the non calcified cartilage, leading new bone formation. Simultaneously, new cartilage cells are proliferating in the superficial layers of the non calcified cartilage, which continues to grow. This process leads to changes in the shape of the articulating bone ends and the overlying cartilage and thus the shape of the joint ({1}. After the growth period ends, the trabecular bone, subchondral bone plate, calcified cartilage, and non calcified cartilage continue responding to changes in biomechanical forces in the joint {2-7}. Advancing tide mark and multiple tide marks have been documented in multiple early OA studies ({8-9}. The advancement in the tide mark has also been documented in early OA both in experimental and in human studies using plain films and histology {10-13}. Further, microcracks, local cracks in the calcified cartilage extending into the subchondral bone plate are early phenomena in bone remodeling, an enchondral bone formation, and an early feature of OA {14-19}.

The advancing tide mark and ossification of calcified cartilage increase the thickness of the subchondral bone plate. However, since the tide mark moves into the cartilage, this phenomenon decreases the thickness of the cartilage from below. {15, 16, 18, 20-22}. Observed advancement in calcified cartilage is seen in early phase of OA; earlier than the formation of marginal osteophytes {10} and based on experimental studies, earlier than the appearance of non calcified cartilage defects. Microcracks in calcified cartilage extending to the subchondral are also seen preceding the cartilage changes. {23-24}

How are these events related to imaging biomarkers?

The advancing tide mark along with the ossification of the calcified cartilage changes the shape and smoothness of the articulating bones and their articulating surfaces. Those changes include flattening of tibia plateau; step wise changes in articulating bones, central osteophytes, increase in the diameter and surface area of the subchondral bone plate {25-27}. Bone shape changes may precede cartilage changes.

Suggestion

The newer MRI image analysis methods segment the structures in MR images into 3-dimensional objects. That allows computation of their shape parameters, including curvature, and roughness. The use of these new parameters both in animal and human OA studies could provide us information about the sequence of the above mentioned events and how they relate to cartilage loss.

References will be provided at the meeting.

FROM HEALTHY TO OSTEOARTHRITIC KNEE JOINT; THE ROAD TO BE TRAVELLED

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Why definition of the normal knee joint may matter

We know how MR images of the healthy knee appear. We also know what the osteoarthritic knee looks like. Our diagnosis is based on the appearance of the features in bones and cartilage in MR images. However, we do not know how these features change and behave in the early phase of the disease when the knee starts changing from healthy to not healthy. The reason for that is that we do not have clear definitions for the features of healthy anatomic structures of the knee. To be able to really evaluate the effect of therapies in clinical trials we need to be able to measure their effect also on the early phase of the disease.
Since OA is a disease of the knee joint, when we create a definition for the features of the normal knee, we need to include the characterization of the features of all knee joint structures in the final version. However, this is a very demanding task and therefore should be done in phases, where the features of more obvious structures and their components are first characterized. Those structures probably will be cartilage and the bones. The components of knee cartilage plates are non calcified cartilage and calcified cartilage. The components of the bones are: each bone as a whole structure, and each bone's components, including trabecular bone and subchondral bone plate. So all the features of all these components need to be defined.

Why change over time may not be the only way

So far all the quantitative analysis efforts have concentrated on comparing follow up measurements to the base line measurements; in other words they have concentrated on the change over time. Perhaps this is not the only way to address the progression or lack of it in clinical trials or in longitudinal studies. Surely this approach does not address the question of the stage of the disease. Another option would be to quantify the joint's parameters and then compare those values to established normal values. For that purpose, however, we need to establish the accepted range of normal values. Further, if in the future we want to address the effect of different drugs/treatments on different degrees of severity of the disease, we also need to have the accepted range of values for different disease severities.

The road to be traveled

Quantitative image analysis technology has evolved significantly over the last decade. More advanced methods segment most of the anatomic structures of the knee into 3-dimensional objects. All analysis methods provide cartilage volume and thickness per plate, while some provide joint fluid and bone marrow edema volumes, dGEMRIC analysis provide GAG index among other measurements. Regardless of the advancements in the field, before quantitative image analysis will truly benefit the drug development industry, we need to 1) know and define the features of the normal structures of the knee, 2) identify the features in these structures that changed in OA, 3) decide which parameters reflect the state of these features 4) develop analysis software to measure them, 5) define the range of normal values for the measurements and 6) define the range of values associated with severity.
As soon as we have the parameters for the healthy knee structures and have tools to analyze them we can start quantifying them in normal and OA populations to create the range of normal values and for different severities. Then we will have the system we need to accelerate drug development.

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DELAYED GADOLINIUM MRI OF CARTILAGE (dGEMRIC) FOR ASSESSMENT OF CARTILAGE MATURATION AFTER REPAIR SURGERY: CLINICAL PROTOCOL USING FAST SEQUENCE TECHNIQUE, VALUE OF NON-CONTRAST AND COMPARISON OF DIFFERENT THERAPIES

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INTRODUCTION: For MR imaging of cartilage repair morphologic scores allow visualization of the filling of the defect by repair tissue, the surface of the implant and the integrity to the adjacent native cartilage and bone. Besides this morphologic basic information, biochemical information on the maturation is desirable to get more information on tissue properties of repair tissue. T_1 mapping with delayed Gadolinium Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC) proved to be a potential tool to reflect biochemical structure of cartilage by visualization and quantification of glycosaminoglycan (GAG). Since GAG are related to biomechanical properties in cartilage dGEMRIC in cartilage repair seems to be highly attractive.

OBJECTIVE: The study covered three main questions: 1. to define the potential of dGEMRIC in a longitudinal one year follow-up study of patients after matrix-associated autologous chondrocyte transplantation (MACT) 2. to evaluate the zonal distribution of GAG in healthy hyaline cartilage and repair tissue by dGEMRIc and 3. the ability of dGEMRIC to differentiate between the composition of repair tissue between two different cartilage repair surgeries: MACT and MFX (Microfracture therapy).

METHODS:

Sixty femoral condyles in 45 patients after MACT and MFX of the knee joint underwent MR scanning at 3T using a multi-channel knee coil at different time points after therapy and 15 patients with MACT in a 1 year follow up were included in the study. Based on the postoperative interval the patients were divided into two groups: group 1 up to 18 month (n = 14) and 2 more then 18 month (n = 16). The imaging protocol included a 3D GRE sequence (VIBE) sequence with two different flip angles for assessment of T1 relaxation times. For dGEMRIC VIBE with two different flip angles was performed before and after i.v.administration of anionic gadolinium DTPA (Magnevist®) with a delay of 60 minutes to allow contrast agent to diffuse cartilage layer completely. Evaluation was performed by two regions of interest (ROI) from deep to superficial layer within the cartilage repair tissue representing the zonal variation and two ROI of healthy appearing cartilage within the same knee joint for comparison. For comparability of therapy, patients from each surgical group were matched by age (MFX: 37.1 +/- 16.3 years; MACT: 37.4 +/- 8.2 years) and postoperative interval (MFX: 33.0 +/- 17.3 months; MACT: 32.0 +/- 17.2 months). The delta relaxation rate (deltaR1) (relaxation rate postcontrast minus relaxation rate precontrast) for repair tissue and normal hyaline cartilage and the relative deltaR1 (delta relaxation rate of repair tissue divided by delta relaxation rate of normal hyaline cartilage) were calculated, and mean values were compared between both groups using an analysis of variance.

RESULTS:

In the follow-up study a significant difference of the mean delta R1 values between repair tissue and normal healthy cartilage in the baseline and in the one-year follow-up examination (p-value < 0.001). There was a significant increase of values respectively a decrease of GAG content from the deep to superficial layer in normal healthy cartilage with almost no variation and significantly higher values for the repair tissue at both examinations. In one-year follow-up there was a 22.7% drop of delta R1 values in the deep zone of the repair tissue. For comparison of therapy the mean deltaR1 for MFX was 1.07 +/- 0.34 versus 0.32 +/- 0.20 at the intact control site, and for MACT, 1.90 +/- 0.49 compared to 0.87 +/- 0.44, which resulted in a relative deltaR1 of 3.39 for MFX and 2.18 for MACT. The difference between the cartilage repair groups was statistically significant.

CONCLUSION: dGEMRIC using a clinical applicable fast T1 with an acquisition time of 4 min allows a zonal visualization of cartilage and cartilage repair tissue, can monitor changes in cartilage maturation after MACT over one year and allows to determine the GAG content in repair tissue after two different cartilage repair surgeries.

Rapid Isotropic 3D-Sodium MRI of Knee Joint In-vivo at 7T

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INTRODUCTION: Loss of glycosaminoglycans (GAG) is a signature of early osteoarthritis (OA). Although sodium MRI has been shown to correlate linearly with GAG concentration [1, 2], it poses major challenges at clinical magnetic field strengths (1.5T/3.0T) in terms of low signal-to-noise (SNR), poor spatial resolution and long acquisition times due to low natural abundance, low sodium concentration and rapid bi-exponential signal T2 decay when compared to proton MRI. High and ultra high field systems (4.0T-9.4T) with improved gradient hardware and pulse sequences have potential in improving the spatial-temporal resolution of sodium MRI of knee in vivo in clinically acceptable scan times. Therefore, the aim of this study was to demonstrate the feasibility of acquiring high resolution, isotropic 3D-sodium MRI of whole knee joint in less than 15 minutes at 7T via 3D-radial acquisition with ultra short echo times.

OBJECTIVE: To acquire high resolution, isotropic 3D-sodium images of the whole knee joint in-vivo with clinically acceptable scan times via 3D-radial acquisition.

METHODS: Five healthy controls (4 males, 1 female; mean age 28) and five OA patients (3 males, 2 females; mean age 52) underwent ^{23}Na–MRI on a 7T whole body imager equipped with multi-nuclei options (Siemens Medical Solutions, Erlangen, Germany). Approval for this study was obtained from our institutional review board (IRB) and informed consent was obtained from all the subjects. All the MRI experiments were performed utilizing a quadrature ^{23}Na knee coil (Rapid MR International, LLC, OH) and a 3D-GRE imaging sequence with radial acquisition (TR = 80 ms, TE = 0.160 ms, BW = 130 Hz, signal averages = 10, with spatial resolutions = 1.5mm - 4mm, radial projections= 512-1024; acquisition times= 13:42 minutes). Five cylindrical calibration phantoms consisting of known sodium concentrations (100 - 300mM) were simultaneously imaged to obtain calibration data to compute cartilage Na^+ concentration as previously described [2]. Compartment wise (Patella, femoral-tibial medial joint, and femoral-tibial lateral joint) sodium concentration was measured in healthy and OA patients. The Student's t-test was calculated to determine the statistical significance.

RESULTS: Representative sodium images with different spatial resolutions were shown in Fig.1. The average SNR for different spatial resolutions (1.5mm-4mm) varies from ~30 - 64 respectively. The mean sodium concentration of healthy subjects ranging from ~240 to 280 mmol/L. However, in OA patients the sodium concentrations were reduced to ~30-60% depending upon the degree of cartilage degeneration. There is a significant difference in sodium concentration between healthy subjects and OA patients (P = 0.00003).

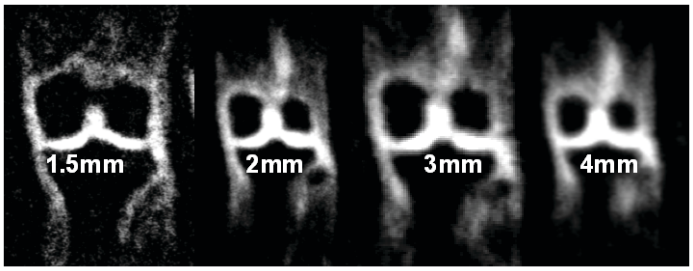

Fig.1

CONCLUSION: This is the first study that demonstrates the feasibility of acquiring high resolution, isotropic 3D-sodium knee images of healthy and OA patients at 7T in less than 15 minutes. The preliminary results suggest that the sodium imaging at 7T may be a viable potential alternative for OA imaging.

REFERENCES: 1). Bashir et al MRM, 41 (1999) 857-65. 2). Shapiro et al JMR 142 (2000) 24-31.
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Quantitative MRI Study of Cartilage Tribology

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Abstract

INTRODUCTION: The morphological features of articular cartilage (AC) are closely related to the health status and the functions of synovial joints. Early detection of any abnormal morphological changes (e.g., degeneration and wear of AC or lesions) is important for diagnosis and treatment of joint diseases, especially osteoarthritis. It is also important in laboratory studies to quantify cartilage wear in order to understand the degeneration of AC. Magnetic Resonance Imaging (MRI) is now widely used in quantitative studies of articular cartilage volume and morphology for its non-invasiveness, relatively high precision and accuracy and 3D delineation. Furthermore, efficient methods for quantitative assessment of cartilage wear are especially important in high-volume studies of cartilage tribology.

OBJECTIVES: The aim of this study was (1) to investigate the capability of MRI in the delineation of the cartilage morphology and detection of subtle wear or lesions; (2) to develop a method to determine wear volumes, based on MATLAB™, and compare it with the one using ANALYZE™ software.

METHODS: Forty-five 18 month old bovine medial femoral condyles were dissected and underwent wear testing, using a pendulum friction simulator. The condyles were articulated against different counterface surfaces (AC, with and without meniscus and stainless steel) under physiologically relevant loading and motion (McCann et al, 2008). Post testing samples were then cut into a smaller specimen which contains the cartilage contact surface (<20 x 20 x 50 mm^3) to fit the MR imaging tube. MR imaging was carried out on Bruker AVANCE™ II 400 MHz 9.4 Tesla laboratory NMR system. A spin-echo sequence was used as the standard protocol for this multi-2D image study due to its high-quality delineation of cartilage morphology, good signal to noise ratio and its acceptable scanning duration (21 min). The TE was set to 10.5 ms, and TR was set to 4843 ms. Spatial resolution ranged from 20 to 78 μm/pixel, and slice thickness was 1mm (with 40 slices in each specimen). The original images were analysed using a MATLAB™ code which was designed to perform the curve fitting and wear volume calculations. The commercial ANALYZE™ software was then used for comparison. (see Figure 1).

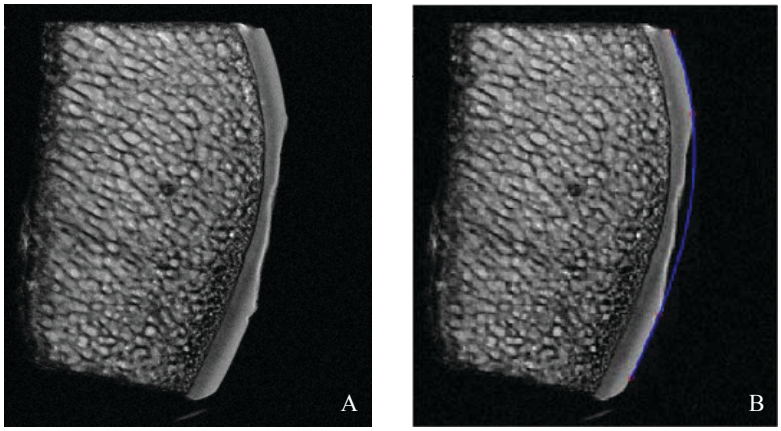

Figure 1. (A) An MR image of the cartilage sample. (B) The curve of the cartilage has been reconstructed by the MATLAB code.

RESULTS: No wear volume was detected in some specimens (n=39), even using a resolution of 20 μm/pixel. For other specimens (n=6), the wear volumes measured both by MATLAB programme and ANALYZE are given in Table 1:

TABLE 1. Wear volumes (mm^3) calculated by MATLAB™ and ANALYZE™ (n=6)

	MATLAB™ PROGRAMME		ANALYZE™	
	Mean	SD	Mean	SD
High Load_AC vs AC (without meniscus)	77.77	23.97	82.89	22.11

CONCLUSION: High field MRI is capable of providing high quality images of articular cartilage and wear volume in in-vitro tribological studies. Two semi-automated methods for the determination of cartilage wear volume used in this study are in excellent agreement with each other. Further studies are required to investigate the reproducibility of these approaches and validate them against a reference method.

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STATISTICAL SHAPE MODELLING REVEALS FOCAL PATTERNS OF CARTILAGE LOSS IN OAI PROGRESSION COHORT

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INTRODUCTION: MRI offers the opportunity to assess the integrity of articular cartilage directly. However, in order for this information to be of most value, it is important to understand the pattern of change as the disease progresses.
OBJECTIVE: To determine 1) the change in cartilage thickness and 2) the distribution of any such change in a 12-month progression group of individuals with knee OA, comparing the pattern in men and women.
METHODS: A convenience group of 50 individuals (29 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. A dense set of anatomically corresponded points was automatically identified on the femur (n=6000) and tibia (n=5000) 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 12m 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:

	All (n = 50)			Females (n = 21)			Males (n = 29)		
	%	SRM	p	%	SRM	p	%	SRM	p
MF	-4.69	-0.723	0.00001	-4.38	-0.740	0.003	-4.89	-0.719	0.001
MT	-2.64	-0.279	0.05440	-2.42	-0.169	0.448	-2.78	-0.489	0.014
LF	0.64	0.145	0.31142	1.73	0.422	0.068	-0.05	-0.011	0.952
LT	-1.37	-0.354	0.01558	-0.93	-0.185	0.406	-1.63	-0.513	0.010

Table 1: % Change in average thickness by compartment, and by sex of subject

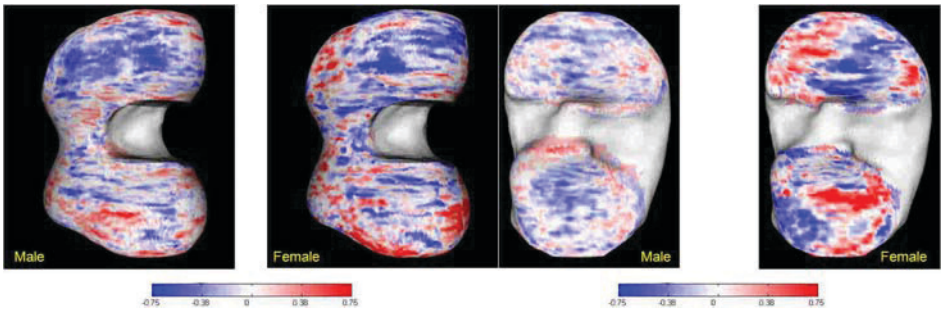

Figure 1: SRM values plotted on mean bone shapes for males and females ((blue = loss of cartilage, red = gain of cartilage over year)

CONCLUSION: The amounts of change in the articular knee cartilage of this OAI progression group agreed well with other published authors The pattern of cartilage loss on both the femur and tibial plateau is broadly within the meniscal window, although the change is focal and variable. Females seem to show greater dynamic range of cartilage thickness gain as well as loss than males. This data suggests the need to treat males and females independently in any clinical study of the disease.

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SPATIAL PATTERNS OF CARTILAGE LOSS IN THE MEDIAL FEMORAL CONDYLE – DATA FROM THE OSTEOARTHRITIS INITIATIVE

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INTRODUCTION: The medial femoral condyle (MF) is frequently separated into a central (weight-bearing, cMF) and a posterior region of interest (pMF). However, it has not yet been shown which region of MF displays the highest and most uniform changes of cartilage morphology over time in OA. Knowledge on the magnitude and sensitivity to change in various subregions of MF may improve the understanding of the natural progression of OA, reveal relations to other structures, such as the meniscus, and reduce the number of participants required for DMOAD studies.

OBJECTIVE: To determine the rate and sensitivity to change of cartilage thickness longitudinally in different subregions of interest within the medial femoral condyle.

METHODS: An algorithm for subdividing the medial femoral condyle (MF) in anterior-posterior direction was developed. Spheres were fitted to the subchondral bone surface (tAB) of MF, to establish a frame of reference (long axis of the femur, intersecting MF at the trochlear notch = 0°). Overlapping regions of 30° (0-30°,15-45°,etc.) were defined from anterior to posterior along MF. In order to avoid artifacts at the edges, these regions were clipped in medial-lateral dimension, to analyze the central 33% and 80% of MF. The algorithm was applied to sagittal baseline and year 1 follow up MR data sets (0.7 mm DESSwe) of 80 participants from the OA initiative (48 women and 32 men from the OAI public-use datasets1.2.1 Clinical Data set and 1.B.1 Imaging Data set; age = 60.6±9.1 yrs.), which had been segmented by 7 experienced users. 47 participants had medial radiographic joint space narrowing (JSN) grade 1, and 32 JSN grade 2 or 3. The standardized response mean (SRM = mean change/SD of change) of cartilage thickness (ThCtAB) was computed for all subregions of MF as a measure of the sensitivity to change

RESULTS: There was a 2.3% reduction in ThCtAB of the total condyle (MF) over one year (SRM =-0.42). The changes tended to be higher in regions 30°-90° than in those< 30° or >90° (Tables 1,2). They were higher in central areas than in those without medial and lateral clipping (Tables 1, 2). The maximal changes in JSN 1 knees were located more posteriorly (45-90°), whereas those in JSN 2/3 knees, more anteriorly (15-75°).

Table 1: Mean change (MC%) for cartilage thickness in the 9 regions of interest of the medial femoral condyle (MF)

MC [%]	0-30°	15-45°	30-60°	45-75°	60-90°	75-105°	90-120°	105-135°	120°150°
No clipping	-2.6	-2.4	-3.4	-3.7	-3.1	-2.0	-1.1	-0.9	-1.3
Central 80%	-2.8	-3.5	-4.0	-4.7	-4.1	-2.8	-1.5	-1.0	-1.4
Central 33%	-3.8	-5.3	-6.6	-7.0	-6.3	-3.9	-1.5	-1.0	-2.3

Table 2: SRM for cartilage thickness changes in the 9 regions of interest of the medial femoral condyle (MF)

SRM	0-30°	15-45°	30-60°	45-75°	60-90°	75-105°	90-120°	105-135°	120°150°
No clipping	-0.27	-0.31	-0.37	-0.45	-0.44	-0.28	-0.16	-0.14	-0.19
Central 80%	-0.29	-0.34	-0.38	-0.50	-0.52	-0.35	-0.21	-0.14	-0.19
Central 33%	-0.30	-0.33	-0.38	-0.47	-0.54	-0.37	-0.17	-0.12	-0.27

CONCLUSION: Cartilage loss in OA is not uniform throughout the femoral condyle. The greatest changes were observed between 30- 90° from the trochlear notch (mainly centrally in the condyle), and smaller changes anteriorly and posteriorly. Further studies may investigate the specific relationship with structural changes in the posterior horn of the meniscus. Interestingly, an anterior shift of the region of maximal change was observed with increasing JSN.

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COMPARISON OF ONE YEAR CHANGE IN MINIMUM JOINT SPACE WIDTH TO FIXED LOCATION JOINT SPACE MEASUREMENTS IN LYON SCHUSS X-RAYS FROM THE A9001140 STUDY

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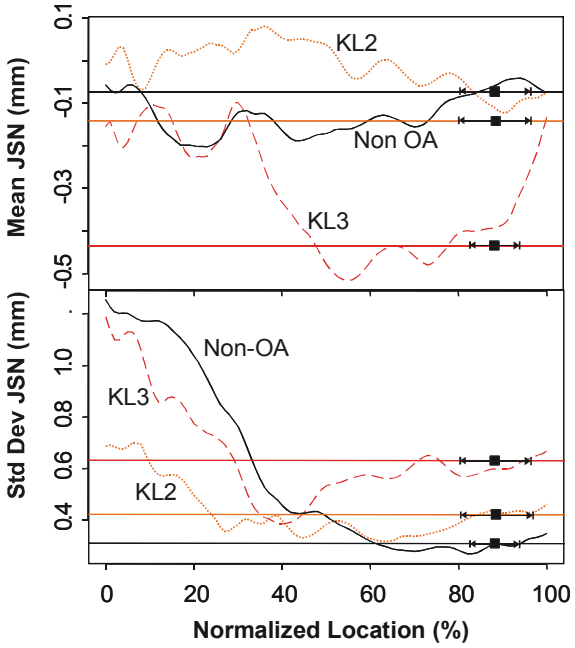
INTRODUCTION: Joint space narrowing (JSN) calculated from the change in minimum joint space width (mJSW) from x-ray has become a valuable tool for the monitoring of progression in osteoarthritis (OA). However, due to the long duration and large number of subjects more sensitive methods are required.

OBJECTIVE: To investigate the relative sensitivity of JSN when measured at fixed locations in Lyon schuss x-rays

METHODS: Lyon schuss x-rays from a subset of 67 subjects from the A9001140 study acquired at 7 sites at baseline and 12 months were analyzed using KneeAnalyzer (Optasia Medical), proprietary statistical model-based analysis software. The femoral and tibial margins of the medial compartment were segmented and JSW was measured along a normalized distance across the medial compartment from 0% at the tibial spine to 100% at the medial margin of the tibia. 31 subjects had Non-OA defined as Kellgren and Lawrence (KL) grades of 0 or 1. The OA subjects had KL=2 (n=17) or KL=3 (n=19). The JSN at the mJSW location and the average JSN between 51%-90% (aJSN 51-90%) were calculated along with the standard deviation (Std Dev) and the standard response mean (SRM). Significance was determined by $p < 0.05$.



RESULTS: Figure 1 shows the mean (top) and standard deviation (bottom) of the JSN for each KL group across the medial compartment. The squares are the location of the mJSW measurement (± one Std Dev). Between 50 and about 85% the profiles are relatively flat indicating a consistent difference in JSN. However, around 90% (the approximate location of mJSW) there is a steep change in the JSN profile for KL3 subjects and a crossing of the Non OA and KL2 plots. The Std Dev of the measurements, are relatively consistent from 50 to 100%.

	mJSW narrowing				aJSN 51-90%			
	Mean	Std Dev	SRM	p	Mean	Std Dev	SRM	p
Non OA	-0.07	0.31	-0.24	0.20	-0.12	0.25	-0.48	0.01
KL2	-0.14	0.42	-0.34	0.19	-0.04	0.34	-0.12	0.62
KL3	-0.43	0.63	-0.69	0.008	-0.45	0.56	-0.80	0.003

CONCLUSION: This study is unique in that it measured the JSN profile from Lyon schuss X-rays. The range of 51%-90% for the aJSN measurements was chosen because it was an area of fairly consistent narrowing as well as low Std Dev for the measurements. For KL3, both mJSN and aJSN 51-90% showed significant change but the latter had a higher SRM and hence is potentially more sensitive. While the Non-OA had a significant and unexpected change in aJSN 51-90% it should be noted that direct comparisons between the two methods were not significantly different. The aJSN measures may provide additional information regarding OA progression in the medial compartment to mJSW narrowing alone and further investigation is warranted to determine how these measures reflect the complicated underlying biological progression of OA.

SPONSOR: Pfizer Inc.
DISCLOSURE STATEMENT: E.V. Consults for Pfizer
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REORGANIZATION OF THE EXTRACELLULAR MATRICES IN COMPRESSED CARTILAGE BY POLARIZED LIGHT MICROSCOPY AND FOURIER-TRANSFORM INFRARED IMAGING

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INTRODUCTION: Articular cartilage has distinct depth-dependent properties across its (thin) thickness. In the simplest sense, the tissue is sub-divided into three histological zones based on the local orientation of the collagen fibrils. It is this orientational structure of the collagen fibrils that results in the tissue's depth-dependent anisotropy as measured by various imaging techniques. Compression will inevitably result in the deformation of the collagen matrix, which will change the molecular anisotropy.

OBJECTIVE: To resolve the depth-dependent consequences of static loading in articular cartilage.

METHODS: Fifteen articular cartilage-bone specimens were compressed in the strain range of 0% to 50%. The deformation of the extracellular matrices in cartilage was preserved [1] and the same tissue sections were studied using polarized light microscopy (PLM) and Fourier-transform infrared imaging (FTIRI). For each of the fifteen specimens, three to five of the unstained sections were imaged in a PLM, which allows the calculation of two quantitative images, representing the optical retardance and the angular orientation of birefringent elements in the tissue [2]. In order to quantify the infrared anisotropy, one representative section from each of the fifteen specimens was imaged in a FTIRI nineteen times, each time with the identical experimental parameters except a 10° angle increment of the analyzer [3].

RESULTS: The PLM results show that the most significant changes in the relative zone thickness due to 're-organization' of the collagen fibrils based on the birefringence occur between 0% to 20% strain values, where the increase in the superficial zone and decrease in the radial zone thicknesses are approximately linear with the applied strain (Fig1). The FTIRI anisotropy results show that the two amide components with bond direction perpendicular to the external compression retain anisotropy (amide II in the superficial zone and amide I in the radial zone). In contrast, the measured anisotropy from the two amide components with bond direction parallel to the external compression change their anisotropy significantly (amide I in the superficial zone and amide II in the radial zone) (Fig2). Statistical analysis shows that there is an excellent correlation (r=0.98) between the relative depth of the minimum retardance in PLM and the relative depth of the Amide II anisotropic crossover (Fig3).

Fig 1 PLM Zone Reorganization

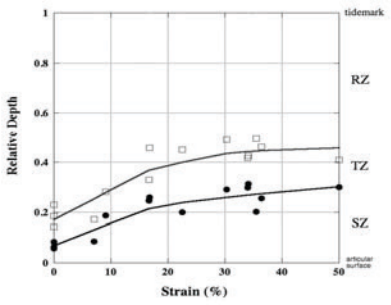


Fig 2 FTIRI Amide Adaptations

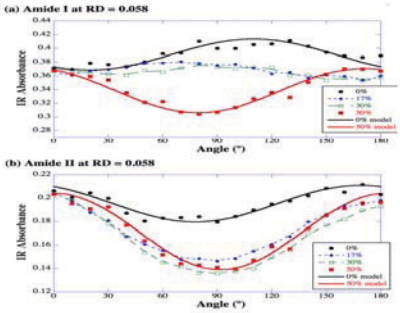
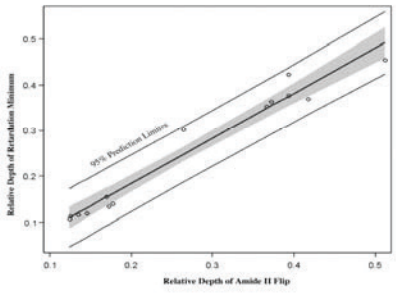


Fig 3 PLM vs FTIRI



CONCLUSION: This work provides the foundation for future study of molecular and morphological modification in the early diseased cartilage, since the modification and weakening of the fibril structure in the tissue often signals the onset of cartilage degradation.

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MULTIDISCIPLINARY VIEW OF THE DEPTH-DEPENDENT PROPERTIES OF ARTICULAR CARTILAGE

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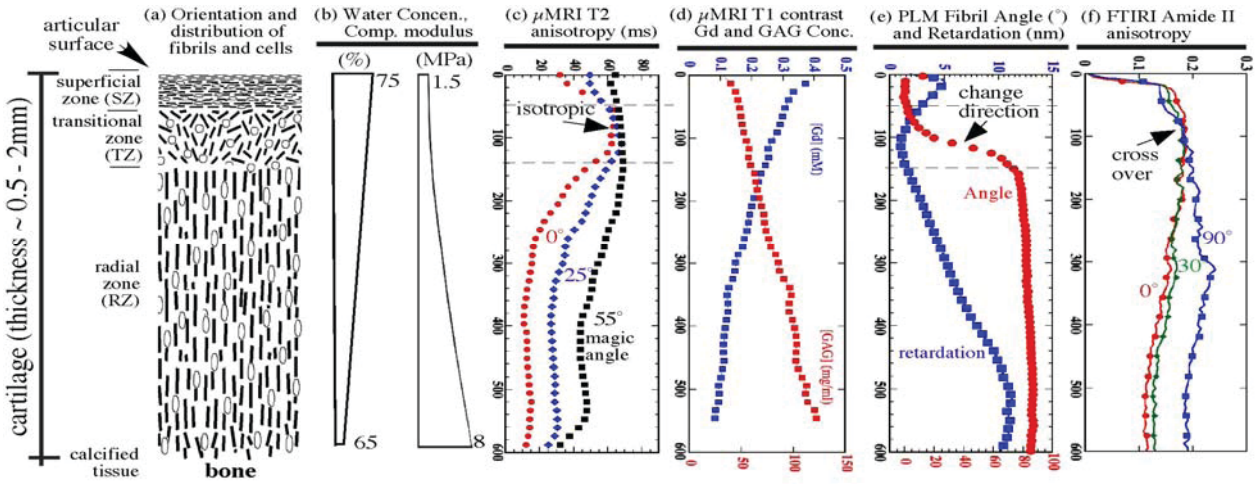
INTRODUCTION: Articular cartilage has been studied in recent years by a number of microscopic imaging techniques, including microscopic MRI (μMRI), polarized light microscopy (PLM), Fourier-transform infrared imaging (FTIRI), and electron microscopy (eg TEM). Each of these imaging techniques can offer some type of characterization of the tissue's depth-dependent properties and structures.

OBJECTIVE: To correlate the depth-dependent properties and structures of cartilage from multidisciplinary imaging techniques in order to gain deeper appreciation of the tissue.

METHODS: We pool together [1] several of our recent imaging works [3-6], which have used essentially the same type of canine cartilage from humeral heads. We compare these imaging results with the biomechanical results in literature [2]. An ellipse model was developed [1] as a common platform to correlate these multidisciplinary results.

RESULTS: The following figure summarizes our current, state-of-the-art understanding of articular cartilage, which contains many correlations among these multidisciplinary works. Because cartilage at different depths can have a unique combination of structures and properties (eg, bio-electrochemical composition, solid/fluid interaction, morphological architecture, mechanical property), it is found that many aspects of these depth-dependent tissue properties can be interpreted beyond their usual meanings as measured. In addition, although it is common in histology to divide non-calcified cartilage into three discrete zones, the physical properties, chemical composition, and morphological features of articular cartilage vary ***continuously*** across its thickness. Therefore the definition of discrete cartilage zones in histology merely represents a conceptual 'discretization' of these continuous functions.



CONCLUSION: Applying the multidisciplinary techniques can discriminate among the various molecular and ultrastructural changes and their influence on the functional integrity of cartilage as a load-bearing material.

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ACKNOWLEDGMENT: Members of the Xia Lab who did the original experimental work.
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IMAGING-BASED MEASURES OF EARLY OSTEOARTHRITIS ARE POSSIBLE, IF YOU HAVE MICROSCOPIC RESOLUTIONS.

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Are the imaging-based measures of early osteoarthritis currently possible (or reliable) [1]? The answer seems to be dependent upon where you come from: NO if you work in a clinical environment, but YES if you work in labs with the capability of imaging at microscopic resolutions [eg, 2,3].

SO, WHAT ARE THE OBSTICLES BETWEEN THE YES AND THE NO?

(1) Articular cartilage is thin and has a depth-dependent heterogeneity across its (thin) thickness (the histological zones).

- *Different structures and molecular environments would be averaged in a bulk or low-resolution MRI measurement.*

(2) Cartilage curves as a 2D surface at the ends of bones in synovial joints and also has various topographical variations in its biomechanical, physical, morphological, and molecular properties.

- *Identifying the precise sampling site where the measurement is done is critically important.*

(3) The earliest detectable lesion tends to be localized and small.

- *High-resolution imaging is needed to characterize the precise nature of the lesion.*
- *At the same time, unless we know the precise location of the early lesion, a wide field of view is needed to survey the joint surface in order to identify any localized lesions.*

(4) The physical conditions (eg, orientation, loading) of the collagen fibrils can cause the cartilage tissue to behave differently in MRI when the same tissue is oriented/loaded differently in the magnet.

- *The orientation of the specimen (including human) in the magnet becomes critically important.*
- *The loading of a joint can also influence the imaging-base measures.*

(5) The degradation of cartilage is an insidious and continuing process, characterized at different degradation stages by different types of structural and molecular changes.

- *Some of these changes may co-exist 'intrinsically' while others co-exist because of multiple environments.*

ARE THERE ROADS TO CONVERGENCE?

Although the currently available imaging-based measures are not perfect, they can detect a number of changes in early arthritis, if the measurement conditions are highly controlled. There exist considerable challenges in adapting these existing measures to the clinical environment, which are the limiting factors in current MRI practices. To make the imaging-based detectability a reliable reality in the clinical environment, two general directions are:

(1) Developing measures that are sensitive to specific events during the early lesions [4],
(2) Developing high-resolution imaging approaches in the clinical environment [5].

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Assessment of Cartilage Morphology and Composition in a Rat Joint Degradation Model via EPIC-μCT

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INTRODUCTION: Sulfated glycosaminoglycan (sGAG) content is an important indicator of the progression and treatment of osteoarthritis. Our previous study indicated that a novel imaging technique based on measuring the Equilibrium Partitioning of an Ionic Contrast agent via microcomputed tomography (EPIC-μCT) was able to assess cartilage morphology and sGAG content in normal and digested cartilage (by Chondroitinase ABC) in rat femoral articular cartilage, providing high resolution spatial images of degeneration patterns. The principle of EPIC-μCT is that a negatively charged, radioopaque contrast agent will be preferentially excluded from regions of higher negative fixed charge density associated with higher sGAG content.

OBJECTIVE: This study investigated whether EPIC-μCT was able to assess cartilage morphology and *in situ* sGAG content in rat articular cartilage during the progression of osteoarthritis after intra-articular administration of monosodium iodoacetate (MIA).

METHODS: Four male 8-week old Wistar rats were anaesthetized with isoflurane, and 1mg of MIA in 50μl saline was injected through the infrapatellar ligament of the right knee, with the left knee injected with saline as a control. The rats were euthanized 1 or 3 week (n=2 each), and both hind limbs were harvested. The distal femur from each limb was incubated in 40% Hexabrix/60% PBS for 30 min at 37ºC and scanned on a μCT-40 system (Scanco) at 45 kVa, 177 mA, 200-ms integration time, and a voxel size of 16 μm.

RESULTS: Consistent with our previous studies, we were able to segment and therefore separately analyze cartilage and bone in the three-dimensional images. One week after injection, the attenuation of MIA-injected femoral cartilage was 26% higher than controls (n=2) without gross morphological changes. Three weeks after injection, cartilage attenuation was 15% higher than controls, while cartilage volume and surface area were 12% and 24% lower, separately. The trabecular bone fraction (BV/TV) in the femoral epiphysis was 14% lower than controls.

CONCLUSION: These data indicate that EPIC-μCT is able to assess cartilage morphology and sGAG content in the rat arthritis model. The capability for EPIC-μCT to analyze cartilage and bone simultaneously will benefit the studies of the interactions between cartilage and bone during the progression of osteoarthritis.

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AUTOMATIC BONE REGISTRATION FOR CARTILAGE MORPHOLOGICAL ANALYSIS ON KNEE MR IMAGES FROM OSTEOARTHRITIS INITIATIVE (OAI)

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INTRODUCTION: The analysis of morphological cartilage degeneration in follow-up MR image studies is essential to guide and monitor the therapies of osteoarthritis. For this, automatic cartilage matching is required prior to cartilage morphological comparison.

OBJECTIVE: To compare the knee cartilage morphology of the same patient at different time points, we propose a cartilage matching technique based on the registration of the corresponding bone structures instead of using the cartilage.

METHODS: Sagittal knee images (repetition time[TR] ms/echo time [TE] ms/flip angle = 16.31/4.71/25°) of eight patients were obtained at 3T MR with an in-plane resolution of 0.36mm x 0.36mm and slice thickness of 0.7mm. Our cartilage matching method consists of five steps. First, cartilage and corresponding bone structures are extracted by region-based semi-automatic segmentation. Second, gross translational mismatch between corresponding bone structures is corrected by point-based rough registration. The center of inertia (COI) of each segmented bone structure is considered as the reference point. Third, the initial alignment is refined by distance-based surface registration. For fast and robust convergence of the distance measure to the optimal value, a 3D distance map is generated by the weighted narrow-band distance propagation. Fourth, affine transformations of the bone surface registration are applied to the cartilage of baseline MR images. Finally, morphological differences of the corresponding cartilages are visualized by color-coded mapping and image fusion.

RESULTS: Femur and femoral cartilage of baseline and follow-up MR images have been used for the performance evaluation with the aspects of visual inspection, accuracy and processing time. After registration, the average Euclidean distance difference of the corresponding femur surfaces in initial misalignment is reduced from 3.69mm down to 1.81mm. All our registration process is finished within one minute.

CONCLUSION: We have developed an automatic cartilage matching technique based on the registration of corresponding bone structures. Our method can be used to monitor the progression of joint diseases or related treatments in osteoarthritis.

SPONSOR:

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REGIONAL CHNAGES OF T1ρ RELAXATION ON PORCINE PATELLAR CARTILAGES IN VITRO BY MEANS OF DEGRADATION ENZYMATICALLY

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INTRODUCTION: In OA, the earliest changes occur in the superficial cartilage and those changes can be highly localized. The biochemical measurements from the whole uncalcified cartilage were not sensitive enough to reveal spatially localized changes. Early OA is characterized by a significant PG loss in the cartilage. Proton exchange between chemically shifted NH and OH groups of PG and water in the cartilage tissue could be an important relaxation mechanism contributing to T1ρ relaxation . Therefore, T1ρ may be specific to changes of PG in cartilage matrix during early stages of OA. T1ρ relaxation can quantitatively measure changes in PG content and previous in vitro. Our hypothesis is that there would be an increase in T1ρ values in early degenerative cartilage compared to normal controls. The aim of the present study was to quantify T1ρ relaxation in various regions of porcine patella cartilage.

OBJECTIVE: To investigate signal changes in spin-lattice relaxation in the rotating frame (T1ρ) from porcine articular cartilages after the trypsin digestion in vitro.

METHODS: T1ρrelaxation times were measured from porcine patellar cartilage. The samples (n = 20) were assigned to 2 groups. A group of right patellar samples (n=10) were immerced in PBS to serve as self-control group. The left patellar samples (n=10) were immerced in PBS with trypsin for 4 hours as treated groups. T1ρ-images were collected with a spin-echo sequence pre-encoded with a spin-lock pulse cluster and a spin-echo sequence on a 7.0T scanner. Using a home-built analysis program, T1ρ- maps were obtained and the cartilage from each sample was manually segmented by drawing regions-of-interest. This segmentation separated the patellar cartilage into four layers (superficial, middle, deep and calcified), which represented the superficial, transitional, radial, calcified zones respectively, to investigate regional differences of T1ρ in patellar cartilage.

RESULTS: T1ρ relaxation in superficial layers ($P<0.05$) increased significantly in samples after 4 hours trypsin digestion. However, T1ρ relaxation showed no difference on both deep and calcified layers in the control groups.

CONCLUSION: This study demonstrates that T1ρ relaxation changes at the articular cartilage with a hyperintense lamina are sensitive to typsin digestion, which might correlate to PG loss and increased water content. Thus, T1ρ measurements could be used as non-invasive early evaluation method for cartilage disease.

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Why Aren't We There yet?

Re-examining Standard Paradigms in Imaging of OA

2nd Annual Workshop on Imaging Based Measures of Osteoarthritis

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Notes