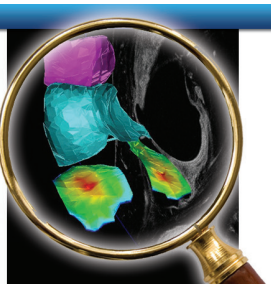


OABiomarker Global Initiative

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

6th International Workshop on Osteoarthritis Imaging combined with the OARSI OA Biomarkers Workshop III - Imaging Biomarker Validation and Qualification

Meeting Chairs: David Hunter, MBBS, PhD, FRACP, Ali Guermazi, MD

Scientific Program Committee: Felix Eckstein, MD, Virginia Byers Kraus, MD, PhD, Elena Losina, PhD, Linda Sandell, PhD

July 12-14, 2012 • Hilton Head Marriott Resort & Spa • Hilton Head Island, South Carolina, USA

FINAL PROGRAM

Wednesday, July 11

7:00 PM – 9:00 PM *Ballroom G*	**Speaker and Sponsor Dinner (by invitation only)**

Thursday, July 12

8:00 AM – 9:30 AM *Ballroom Foyer West*	**Breakfast**
9:30 AM – 12:30 PM *Ballroom J*	**Pre-Course - Workshop on the Practical Use of Imaging Biomarkers in Clinical Studies/Trials** **Ali Guermazi, MD, Colin Miller, PhD, FICR, CSci & Matthew Shive, PhD** Optimal image analysis is reliant on optimal acquisition and careful quality control. This will be a practical and interactive session to help you with the questions you need to consider in study/clinical trial planning. The session will discuss and invite attendees to workshop issues including: • Selection and qualification of sites • Designing imaging protocols for whole organ assessment • Image quality control and data management
12:30 PM – 2:00 PM *Sabal Palm Room*	**Lunch**
2:00 PM – 2:30 PM *Ballroom J*	**Introduction** Chair: David Hunter, MBBS, PhD, FRACP Welcome and Themes of the Workshop – What is Required for Validation and Qualification? **Sahar Dawisha, MD & Michael Nevitt, PhD, MPH**
2:30 PM – 4:00 PM	**Module 1: Overview of Imaging Techniques**
2:30 PM – 3:00 PM	Overview of Current Imaging as Applied to OA Diagnostics and Clinical Studies: What Methods are Currently Used and What are the Limitations? **Frank Roemer, MD**

3:00 PM – 3:15 PM 1. THE ASSOCIATION BETWEEN CLINICAL OUTCOME AND CHANGE OF CARTILAGE THICKNESS AND TOTAL AREA OF SUBCHONDRAL BONE OVER TWO AND FIVE YEARs IN A TREATMENT RCT OF PATIENTS WITH ACUTE ANTERIOR CRUCIATE LIGAMENT INJURY

R.Frobell[1], W. Wirth[2], L.S. Lohmander[1], M. Hudelmaier[2], F. Eckstein[2]

[1] Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden, [2] Paracelsus Medical University, Salzburg, Austria & Chondrometrics GmbH, Ainring, Germany

3:15 PM – 3:30 PM 2. QUANTITATIVE BONE MARROW LESION CHANGES RELATE TO CARTILAGE PARAMETER CHANGES: DATA FROM THE OSTEOARTHRITIS INITIATIVE

J. B. Driban[1], J. Pang[2], E. Miller[2], G. Destenaves[1], G. H. Lo[3], R. J. Ward[1], L. L. Price[1], C. B. Eaton[4], T. E. McAlindon[1]

[1]Tufts Medical Center, Boston, MA, USA, [2]Tufts University, Medford, MA, USA, [3]Michael E. DeBakey VA Medical Center / Baylor College of Medicine, Houston, TX, USA, [4]Center for Primary Care and Prevention, Alpert Medical School of Brown University, Pawtucket, RI, USA

3:30 PM – 3:45 PM 3. SYMMETRIC PREVALENCE OF CARTILAGE DAMAGE, BONE MARROW LESIONS AND MENISCAL LESIONS IN SUBJECTS WITH KNEE PAIN: THE JOG STUDY

F.W. Roemer[1,2], C.K. Kwoh[3], M.J. Hannon[3], R.M. Boudreau[3], S.M.Green[3], J.M. Jakicic[3], C.M. Moore[4], A. Guermazi[1]

[1]Boston University, Boston, MA, [2]Klinikum Augsburg, Augsburg, Germany, [3]University of Pittsburgh, Pittsburgh, PA, [4]Texas Woman's University, Houston, TX

3:45 PM – 4:00 PM 4. THE ASSOCIATION BETWEEN RADIOGRAPHIC HAND OSTEOARTHRITIS, MENISCAL DAMAGE, AND TORN ANTERIOR CRUCIATE LIGAMENT

M. Englund [1, 2], I. K. Haugen [3], A. Guermazi [4], F. W. Roemer [5], J. Niu[2], T. Neogi [2], P. Aliabadi [6], D. T. Felson [2]

[1]Dept of Orthopedics, Lund University, Lund, Sweden, [2]Clinical Epidemiology Research & Training Unit, Boston University School of Medicine, Boston, United States, [3]Diakonhjemmet Hospital, Oslo, Norway, [4]Dept of Radiology, Boston University School of Medicine, Boston, United States, [5]Dept of Radiology, Klinikum Augsburg, Augsburg, Germany, [6]Brigham & Women's Hospital, Boston, United States

4:00 PM – 4:30 PM
Ballroom Foyer West

Break

4:30 PM – 6:00 PM
Ballroom J

Module 2: Update on Molecular Biomarkers
Chair: Linda Sandell, PhD

4:30 PM – 5:00 PM

Update on Molecular Biomarkers
Virginia Byers Kraus, MD, PhD

5:00 PM – 5:15 PM 5. THE ABILITY OF BIOCHEMICAL MARKERS TO REFLECT (VERY) EARLY RADIOGRAPHIC KNEE AND HIP OSTEOARTHRITIS: DATA FROM CHECK, A COHORT OF EARLY OSTEOARTHRITIS.

W.E. Van Spil[1], N.W.D. Jansen[1], J.W.J. Bijlsma[1], P.M.J. Welsing[1], F.P.J.G. Lafeber[1]

[1]Rheumatology and Clinical immunology, University Medical Center Utrecht, Utrecht, The Netherlands

5:15 PM – 5:30 PM	6.	COLLAGEN BIOMARKER RESPONSE TO ACUTE JOINT INJURY IN A NON-TERMINAL ANIMAL MODEL OF OSTEOARTHRITIS M. Boyce[1], **T.N. Trumble[1]**, D.M. Groschen[1], K.A. Merritt[2], M.P. Brown[2] [1]University of Minnesota, St. Paul, MN, USA, [2]University of Florida, Gainesville, FL, USA
5:30 PM – 5:45 PM	7.	GWAS OF OSTEOARTHRITIS BIOMARKERS SERUM HYALURONIC ACID AND CARTILAGE OLIGOMERIC MATRIX PROTEIN IMPLICATES FOXN4, ETV6, KIAA1217, ZNF521, SPHKAP, AND CSGALNACT1 H.B. Coan[1], A. Choudary[1], D.P. Nicolella[2], T.D. Dyer[1], J.E. Curran[1], M.C. Carless[1], S. Kumar[1], J.S. Kent Jr.[1], L.A. Almasy[1], H.H. Goring[1], J. Blangero[1], M.C. Mahaney[1], **L.M. Havill[1]** [1]Texas Biomedical Research Institute, San Antonio, TX [2]Southwest Research Institute, San Antonio, TX
5:45 PM – 6:00 PM	8.	BIOPSIES AND IMAGING AT ACL RECONSTRUCTION **D.R. Pedersen[1]**, J.A. Martin[1], N.F. Klocke[1], N.H. Roberts[1], D.R. Thedens[2], G.L. Williams[3], A. Amendola[1] [1]Department of Orthopaedics and Rehabilitation, [2]Department of Radiology, and [3]Department of Physical Therapy, The University of Iowa, Iowa City, IA, USA
6:00 PM – 7:00 PM *Sabal Palm Room*		**Poster Session**
8:00 PM – 10:00 PM *Basshead Deck*		**Dinner - "Australia meets Carolina" (ticketed)**

Friday, July 13

8:00 AM – 9:00 AM *Ballroom Foyer West*	**Breakfast**
9:00 AM – 10:30 AM *Ballroom J*	**Module 3: Perspectives of Need** Chair: Virginia Byers Kraus, MD, PhD
9:00 AM – 9:30 AM	Clinician's Perspective of Needs of the Field **Stefan Lohmander, MD, PhD**
9:30 AM – 10:00 AM	Industry Perspective of Needs of the Field **Marie-Pierre Hellio Le Graverand, MD, PhD**
10:00 AM – 10:30 AM	Discussion
10:30 AM – 11:00 AM *Ballroom Foyer West*	**Break**
11:00 AM – 12:15 PM *Ballroom J*	**Top Rated Abstracts from Young Investigators** Chair: Felix Eckstein, MD **Young Investigator Awards Co-Sponsored by EMD Serono, Inc and Sanofi Biosurgery**

11:00 AM – 11:15 AM	9.	ASSOCIATION OF MR RELAXATION TIMES WITH MUSCLE MORPHOLOGY AND FUNCTIONAL LOADING AT THE KNEE **D. Kumar[1]**, K. Subburaj[1], X. Li[1], T.M. Link[1], R.B.Souza[1,2], S. Majumdar[1]; [1]Musculoskeletal Quantitative Imaging Research Group, Radiology, University of California San Francisco, CA, USA, [2]Department of Physical Therapy, University of California San Francisco, CA, USA
11:15 AM – 11:30 AM	10.	ACUTE ANTERIOR CRUCIATE LIGAMENT INJURY CAUSES CARTILAGE THICKNESS INCREASE OVER TWO AND FIVE YEARS **W. Wirth[1]**, F. Eckstein[1], L.S. Lohmander[2], M. Hudelmaier[1], R.Frobell[2] [1]Paracelsus Medical University, Salzburg, Austria & Chondrometrics GmbH, Ainring, Germany, [2] Orthopedics, Clinical Sciences Lund, Lund University, Lund, Sweden
11:30 AM – 11:45 AM	11.	SUSCEPTIBIILTY ARTIFACTS IN THE TIBIO-FEMORAL JOINT SPACE ON 3T KNEE MRI: FREQUENCY, LONGITUDINAL FOLLOW-UP AND THEIR RELATION TO MENISCAL TEARS, RADIOGRAPHIC JOINT SPACE NARROWING AND CALCIFICATIONS **D. Hayashi[1]**, M. Jarraya[1], A. Guermazi[1], C.K. Kwoh[2,3], M.J. Hannon[2], C. Moore[4], J.M. Jakicic[2], S. Green[2], F.W. Roemer[1,5] [1]Department of Radiology, Boston University, Boston, MA, USA, [2]University of Pittsburgh, Pittsburgh, PA, USA, [3]VAPHS, Pittsburgh, PA, USA, [4]Texas Woman's University, Houston, TX, USA, [5]Department of Radiology, Klinikum Augsburg, Augsburg, Germany
11:45 AM – 12:00 PM	12.	RESPONSIVENESS OF QUALITATIVE AND QUANTITATIVE MRI MEASURES OVER 2.7 YEARS **D. Doré[1]**, C. Ding[1,2], J.P. Pelletier[3], J. Martel-Pelletier[3], F. Cicuttini[2], G. Jones[1]; [1]Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia, [2]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia, [3]Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, Canada
12:00 PM – 12:15 PM	13.	QUADRICEPS MUSCLE AND INTERMUSCULAR FAT VOLUME IN THE THIGHS OF MEN IN THE OAI ARE ASSOCIATED WITH PHYSICAL FUNCTION AND KNEE PAIN **K. A. Beattie[1,2]**, M. R. Maly[1], S. Shaker[2], N. J. MacIntyre[1] [1]School of Rehabilitation Science, [2]Dept. of Medicine, McMaster University, Hamilton, ON, Canada
12:30 PM – 1:30 PM *Sabal Palm Room*		**Lunch**
2:00 PM – 3:30 PM *Ballroom J*		**Module 4: Perspectives on Clinical Outcomes of Relevance in OA** Chair: Ali Guermazi, MD
2:00 PM – 2:30 PM		Evidence of Surrogacy - What Imaging Data Predicts the Development of Long Term Clinical Outcomes **C. Kent Kwoh, MD**

2:30 PM – 2:45 PM | 14. A 2-YEAR RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF ORAL SELECTIVE INOS INHIBITOR, CINDUNISTAT, IN PATIENTS WITH SYMPTOMATIC OSTEOARTHRITIS OF THE KNEE

MP. Hellio Le Graverand[1]; R. Clemmer[1]; P. Redifer; [1]R. Brunell[1]; C.W. Hayes[2]; K. Brandt[3]; S. Abramson[4]; P. Manning[5]; C. Miller[6]; and E Vignon[7]
[1] Pfizer Inc, Primary Care Medicines Development Group, Groton, CT, USA; [2]Department of Radiology, Virginia Commonwealth University Health System, Richmond, VA, USA; [3]Kansas University Medical Center, Kansas City, KS; [4]New York School of Medicine, New York, NY; [5]Vasculox, Inc, St Louis, MO; [6]BioClinica Inc., Newtown, PA, USA; [7]Claude Bernard University, Lyon, France

2:45 PM – 3:00 PM | 15. EFFECT OF iNOS INHIBITION ON STRUCTURAL PROGRESSION OF KNEE OA OVER 2 YEARS – DEFINED AS MRI-BASED QUANTITATIVE CARTILAGE THICKNESS CHANGE

F. Eckstein[1], R. J. Buck[2], W. Wirth[1], A. Guermazi[3], R. Clemmer[4], M.-P. Hellio LeGraverand[4]; [1]Paracelsus Med. Univ., Salzburg, Austria & Chondrometrics GmbH, Ainring, Germany, [2]StatAnswers Consulting LLC, Minneapolis, MN, [3]Boston Univ. & BICL LLC, Boston, MA, [4]Pfizer, Groton, CT

3:00 PM – 3:15 PM | 16. CONSIDERATIONS WHEN DESIGNING A DMOAD CLINICAL TRIAL USING RADIOGRAPHY

MP. Hellio Le Graverand[1]; R. Clemmer[1]; R. Brunell[1]; C.W. Hayes[2]; C. Miller[3]; and E Vignon[4]
[1] Pfizer Inc, Primary Care Medicines Development Group, Groton, CT, USA; [2]Department of Radiology, Virginia Commonwealth University Health System, Richmond, VA, USA;[3]BioClinica Inc., Newtown, PA, USA; [4]Claude Bernard University, Lyon, France

3:15 PM – 3:30 PM | 17. IDENTIFYING RADIOGRAPHIC PHENOTYPES OF EARLY KNEE OSTEOARTHRITIS USING SEPARATE QUANTITATIVE FEATURES MIGHT IMPROVE PATIENT SELECTION FOR MORE TARGETED TREATMENT

M.B. Kinds[1,2], **A.C.A. Marijnissen[1],** M.A. Viergever[2], P.J. Emans[3], P.M.J. Welsing[1,4], F.P.J.G. Lafeber[1]
[1]Rheumatology & Clinical Immunology, and [2]Image Sciences Institute, University Medical Center Utrecht, [3]Orthopaedic Surgery, Maastricht University Medical Center, Maastricht, [4]Julius Center for Health Sciences & Primary Care, University Medical Center Utrecht.

4:00 PM – 5:00 PM
Sabal Palm Room
Poster Session

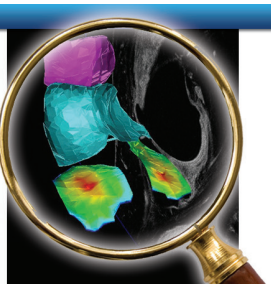
5:00 PM – 6:00 PM
Sabal Palm Room
Corporate Round Table

7:00 PM – 10:00 PM
Basshead Deck
Dinner - "Arabian Nights" (ticketed)

Saturday, July 14

8:00 AM – 9:00 AM
Ballroom West Foyer
Breakfast

9:00 AM – 10:30 AM
Ballroom J
Module 5: Level of Validation of Key Efficacy of Intervention Biomarkers
Chair: Gayle Lester, PhD



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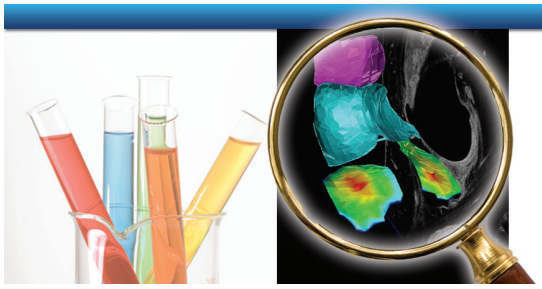
9:00 AM – 9:30 AM		Examination of Construct and Predictive Validity, Reliability and Responsiveness of Key Imaging Biomarkers **Elena Losina, PhD**
9:30 AM – 9:45 AM	18.	FULLY AUTOMATIC CARTILAGE MORPHOMETRY FOR KNEE MRI FROM THE OAI **E. B. Dam[1],** J. Marques[4], S. Zaim[2], T. Fuerst[2], H. Genant[3], M. Lillholm[1], M. Nielsen[1,4]; [1]Biomediq, Copenhagen, Denmark, [2]Synarc, Newark, CA, USA, [3]University of California, San Francisco, CA, USA, [4]University of Copenhagen, Denmark
9:45 AM – 10:00 AM	19.	ADVANCED MRI-BASED BIOMARKERS OF CARTILAGE LOSS: DATA FROM THE OSTEOARTHRITIS INITIATIVE **JG. Tamez-Peña[1,2]** , P Gonzalez [2] , E Schreyer[2] and S Totterman[2] [1]Tecnológico de Monterrey, Monterrey, México, [2]Qmetrics LLC, Rochester, NY, USA
10:00 AM – 10:15 AM	20.	RESPONSIVENESS OF A SEMI-AUTOMATED NOVEL METHOD OF MEASURING CARTILAGE LOSS IN KNEE OSTEOARTHRITIS OVER TWO YEARS USING 3T DESS 3D MRI **J. Duryea[1]**, C. Ratzlaff[1], T. Iranpour-Boroujeni[1], J. Collins[1], E. Losina[1], C. Vanwynngaarden[2], A. Guermazi[3], J. Katz[1]; [1]Brigham and Women's Hosp. / Harvard Med. Sch., Boston, MA, [2]Peace Arch Hosp., White Rock, BC, CANADA, [3]Boston Univ. Sch. of Med., Boston, MA.
10:15 AM – 10:30 AM	21.	IN VIVO DTI OF ARTICULAR CARTILAGE AS A BIOMARKER FOR OA **J. G. Raya[1]**, A. Horng[2], O. Dietrich[2], S. Krasnukotsky[1], L. S. Beltran[1], M. F. Reiser[2], M. Recht[1], C. Glaser[1] [1]New York University Langone Medical Center, New York, NY, USA; [2]Ludwig Maximilians University Hospital Munich; Munich, Germany
10:30 AM – 11:00 AM *Ballroom West Foyer*		**Break**
11:00 AM – 12:15 PM *Ballroom J*		Chair: Elena Losina, PhD
11:00 AM – 11:15 AM	22.	SIGNAL-TO-NOISE IMPACTS THE ACCURACY AND PRECISION OF KNEE ARTICULAR CARTILAGE T2 RELAXATION TIME MEASUREMENTS **B.J. Dardzinski[1]**, E. Schneider[2] [1]Merck Sharp & Dohme Corp., West Point, PA USA, [2]Imaging Institute, Cleveland Clinic, Cleveland, OH USA and SciTrials LLC, Rocky River, OH
11:15 AM – 11:30 AM	23.	VALIDATION OF AN OBJECTIVE, ANALYST-INDEPENDENT, NON-INVASIVE METHOD FOR ASSESSING EFFECTIVENESS OF CARTILAGE REPAIR THERAPIES IN MULTICENTER RCTS **E Schreyer[2]**, M Shive[2], A Restrepo[2], P Gonzalez [1], S Totterman[1] and J Tamez-Peña[1,3] [1]Qmetrics Technologies, Rochester, NY, USA. , [2] Piramal Healthcare (Canada), LTD, Laval, QC, Canada, [3]Tecnologico de Monterrey, Escuela de Medicina. Monterrey, México

11:30 AM – 11:45 AM	24.	LONGITUDINAL CHANGES IN CARTILAGE REPAIR TISSUE QUANTITY AND QUALITY BY QUANTITATIVE MRI **MS Shive[1]**, WD Stanish[2], R McCormack[3], F Forriol[4], N Mohtadi[5], S Pelet[6], J Desnoyers[7], A Restrepo[1] [1]Piramal Healthcare, Laval, Canada, [2]Dalhousie University, Halifax, Canada, [3]University of British Columbia, Vancouver, Canada, [4]CEU Universidad San Pablo, Madrid, Spain, [5]University of Calgary Sports Medicine Center, Calgary, Canada, [6]Centre Hospitalier Affilié Universitaire de Québec (CHAUQ), Québec, Canada, [7] Hôpital Charles-Lemoyne, University of Sherbrooke affiliated, Greenfield Park, Canada
11:45 AM – 12:00 PM	25.	EFFECTS OF TRAINING INTERVENTION ON QUADRICEPS HEADS IN PERI-MENOPAUSAL WOMEN **M Sattler[1]**,T Dannhauer[1,2], S Ring-Dimitriou[3], AM Sänger[4], W Wirth[1,2], M Hudelmaier[1,2], F Eckstein[1,2] [1] Paracelsus Medical University, Salzburg, Austria; [2] Chondrometrics GmbH, Ainring, Germany; [3] Department of Sport Science and Kinesiology, University of Salzburg, Salzburg, Austria; [4] Department of Organismic Biology, University of Salzburg, Salzburg, Austria
12:00 PM – 12:15 PM	26.	COMPARISON OF MUSCLE AREA AND STRENGTH BETWEEN OA KNEES WITH AND WITHOUT STRUCTURAL PROGRESSION - DATA FROM THE OA INITIATIVE **T. Dannhauer[1,2]**, M. Sattler[1], W. Wirth[1,2], D.J. Hunter[3], C.K. Kwoh[4], F. Eckstein[1,2] - for the OAI Investigators [1]Paracelsus Med. Univ., Salzburg, Austria, [2]Chondrometrics GmbH, Ainring, Germany, [3]Univ. of Sydney, Sydney, Australia, [4]Univ. of Pittsburgh and Pittsburgh VAHS, Pittsburgh, PA. USA
12:30 PM – 1:30 PM *Sabal Palm Room*		**Lunch**
1:30 PM – 3:30 PM *Ballroom J*		**Module 6: Designing the Optimal Trials for Understanding OA Panel and Future Directions** **Felix Eckstein, MD, Marie-Pierre Hellio Le Graverand, MD, PhD, David Hunter, MBBS, PhD, FRACP, Virginia Byers Kraus, MD, PhD, Gayle Lester, PhD, Elena Losina, PhD & Linda Sandell, PhD**
3:30 PM – 4:00 PM *Ballroom Foyer West*		**Break**
4:00 PM – 5:30 PM *Ballroom J*		Discussion
7:00 PM – 10:00 PM *Basshead Deck*		**Dinner - "Scandinavian Lights" (ticketed)**

Sunday, July 15

9:00 AM – 3:00 PM	**Tour of Historic Savannah (ticketed)** ***Buses will depart from the hotel at 9:00 AM**



OABiomarker Global Initiative

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

POSTER INDEX

P-1 HOW TO QUANTIFY THE SENSITIVITY OF MRI T1ρ and T2 RELAXATION MEASUREMENT IN CARTILAGE DEGRADATION?
Y. Xia, N. Wang;
Dept of Physics and Center for Biomedical Research, Oakland University, Rochester, MI, USA

P-2 PLASMA LEPTIN AND RESISTIN MAY PLAY A ROLE IN EARLY-STAGE KNEE OSTEOARTHRITIS: DATA FROM CHECK, A COHORT OF EARLY OSTEOARTHRITIS.
W.E. Van Spil[1], P.M.J. Welsing[1], J.W.J. Bijlsma[1], S.C. Mastbergen[1], F.P.J.G. Lafeber[1];
[1]Rheumatology and Clinical immunology, University Medical Center Utrecht, Utrecht, The Netherlands

P-3 CORRELATIONS OF CTX-II WITH BIOCHEMICAL MARKERS OF BONE TURNOVER RAISE QUESTIONS ON ITS TISSUE ORIGIN: DATA FROM CHECK, A COHORT OF EARLY OSTEOARTHRITIS.
W.E. van Spil[1], J.W.J. Bijlsma[1], S.C. Mastbergen[1], F.P.J.G. Lafeber[1];
[1]Rheumatology and Clinical immunology, University Medical Center Utrecht, Utrecht, The Netherlands

P-4 CLUSTERS WITHIN A WIDE SPECTRUM OF BIOCHEMICAL MARKERS FOR OSTEOARTHRITIS: DATA FROM CHECK, A COHORT OF EARLY OSTEOARTHRITIS.
W.E. Van Spil[1], P.M.J. Welsing[1], N.W.D. Jansen[1], J.W.J. Bijlsma[1], F.P.J.G. Lafeber[1];
[1]Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, The Netherlands

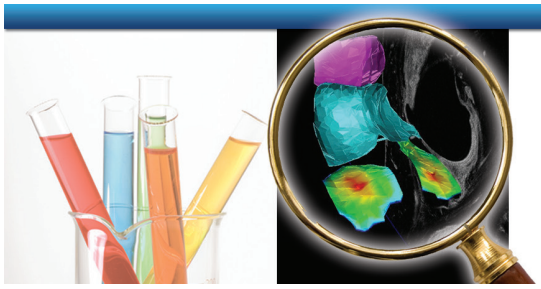
P-5 TIBIAL COVERAGE, MENISCUS POSITION AND SIZE, AND MENISCUS DAMAGE IN CONTRA-LATERAL KNEES WITH AND WITHOUT JOINT SPACE NARROWING - DATA FROM THE OAI
K. Bloecker[1], A. Guermazi[2,3], W. Wirth[1,4], O. Benichou[5], CK. Kwoh[6], DJ. Hunter[7], M. Englund[2,8], H.Resch[1], F. Eckstein[1,2]; for the OAI investigators
[1]Paracelsus Med. Univ., Salzburg, Austria, [2]Boston Univ. Med. Ctr., [2]BICL LLC, Boston, MA, [4]Chondrometrics GmbH, Ainring, Germany, [5]Eli Lilly & Co, Indianapolis, IN, [6]Univ. of Pittsburgh and VAHS, Pittsburgh, PA, [7]Univ. of Sydney, Sydney, Australia, [8]Lund Univ., Lund, Sweden

P-6 EFFECTIVENESS OF HYALURONIC ACID IN KNEE OSTEOARTHRITIS PATIENTS EVALUATED USING DELAYED GADOLINIUM-ENHANCED MRI OF CARTILAGE
J. van Tiel[1,2], M. Reijman[1], P Bos[1], J. Hermans[1], G. van Buul[1], J. Verhaar[1], G. Krestin[2], S. Bierma-Zeinstra[1,3], H. Weinans[1,4], G. Kotek[2], E. Oei[2];
[1]Department of Orthopedic Surgery, Erasmus MC, Rotterdam, The Netherlands, [2]Department of Radiology, Erasmus MC, Rotterdam, The Netherlands, [3]Department of General Practice, Erasmus MC, Rotterdam, The Netherlands, [4]Department of Biomechanical Engineering, Delft University of Technology, Delft, The Netherlands

P-7 PATELLOFEMORAL FRICTION SYNDROME: BIOCHEMICAL CARTILAGE IMAGING USING T2 MAPPING
T.K. Subhawong[1], R.S. Thakkar[1], A. Chhabra[1], S. Demehri[2], J.A. Carrino[1];
[1]Johns Hopkins Hospital, Baltimore, MD, USA, [2]Brigham and Women's Hospital, Boston, MA, USA

P-8 FREQUENCY OF MRI-DETECTED CARTILAGE DAMAGE, OSTEOPHYTES, SUBCHONDRAL CYSTS AND BONE ATTRITION IN PAINFUL HIPS AND THE DIAGNOSTIC PERFORMANCE OF RADIOGRAPHY USING MRI AS THE REFERENCE
D. Hayashi[1], L. Xu[1], A. Guermazi[1], D.J. Hunter[2,3], A. Winterstein[4], L. Li[3], K. Bohndorf[4], F.W. Roemer[1,4];
[1]Department of Radiology, Boston University, Boston, MA, USA, [2] Department of Medicine, University of Sydney, Sydney, Australia, [3]New England Baptist Hospital, Boston, MA, USA[4], Department of Radiology, Klinikum Augsburg, Augsburg, Germany

P-9 READER EXPERIENCE IS AN IMPORTANT FACTOR FOR SEMIQUANTITATIVE ASSESSMENT OF KNEE OSTEOARTHRITIS FEATURES BY TOMOSYNTHESIS; COMPARISON OF RELIABILITY IN READERS WITH DIFFERENT LEVELS OF EXPERIENCE
D. Hayashi[1], L. Xu[1], F.W. Roemer[1,2], D.J. Hunter[3,4], L. Li[4], J. Gusenburg[1], A. Guermazi[1];
[1]Department of Radiology, Boston University, Boston, MA, USA, [2]Department of Radiology, Klinikum Augsburg, Augsburg, Germany, [3]Department of Medicine, University of Sydney, Sydney, Australia, [4]New England Baptist Hospital, Boston, MA, USA



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OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

POSTER INDEX

P-10 MRI-DETECTED SUBCHRONDRAL BONE MARROW SCLEROSIS DOES NOT PREDICT CARTILAGE LOSS IN A COHORT OF SUBJECTS WITH KNEE PAIN: A 3-YEAR FOLLOW-UP STUDY
M.D. Crema[1,2], J. Cibere[3,4], E.C. Sayre[3,4], F.W. Roemer[1,5], H. Wong[4,6], A. Thorne[4,6], J. Singer[4,6], J.M. Esdaile[3], M.D. Marra[1], J.A. Kopec[3], S. Nicolaou[3], A. Guermazi[1];
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P-11 ULTRA-HIGH-FIELD MRI FOR IMPROVING THE ASSESSMENT OF OSTEOARTHRITIS
A. J. Chaudhari[1], D. J. Rowland[2], N. E. Lane[3], M. H. Buonocore[1];
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P-12 FINGER LENGTH RATIOS RELATE TO HAND JOINT SPACE WIDTH IN FEMALES: DATA FROM THE OSTEOARTHRITIS INITIATIVE.
J. Motyl[1], A. N. O'Brien[1], J. Duryea[2], **J. B. Driban[1]**, L. L. Price[1], W. F. Harvey[1], C. B. Eaton[3], T. E. McAlindon[1];
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P-13 VALIDATION OF THREE DIMENSIONAL DUAL-ECHO STEADY STATE SEQUENCE ON 3T MR IMAGING FOR GRADING FOCAL AND DIFFUSE ARTICULAR CARTILAGE LESIONS OF THE KNEE JOINT AS CORRELATED WITH ARTHROSCOPY
R.S.Thakkar[1], T.K.Subhawong[1], F. Del Grande[1], M. Chalian[1], S.C.Thakkar[1], M. Trice[1], A. Padua[2], S. Demehri[1], A. Chhabra[1], **J.A. Carrino[1];**
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P-14 A NEW METHOD TO MEASURE ANATOMIC KNEE ALIGNMENT: A TOOL FOR LARGE STUDIES OF OA
T. Iranpour-Boroujeni[1], J. Li[2], J. Lynch[2], M. Nevitt[2], **J. Duryea[1]**;
[1]Brigham and Women's Hosp., Boston, MA, [2]Univ. of California San Francisco, San Francisco, CA.

P-15 A RAPID, NOVEL, QUANTITATIVE METHOD FOR MEASURING MRI-DETECTED BONE MARROW LESIONS IN KNEE OSTEOARTHRITIS IS COMPARABLE TO WORMS
C. Ratzlaff[1], T. Iranpour-Boroujeni[1], J. Collins[1], J. Katz[1], E. Losina[1], C. Vanwyngaarden[2], A. Guermazi[3], J. Duryea[1];
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P-16 A QUANTITATIVE METHOD FOR MEASURING MRI-DETECTED OSTEOPHYTES IN KNEE OSTEOARTHRITIS: DESCRIPTION OF A NEW METHOD FOR LARGE OA DATASETS
C. Ratzlaff[1], J. Collins[1], J. Katz[1], E. Losina[1], C. Vanwyngaarden[2], J. Duryea[1];
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P-17 NON-TERMINAL ANIMAL MODEL OF EARLY OSTEOARTHRITIS
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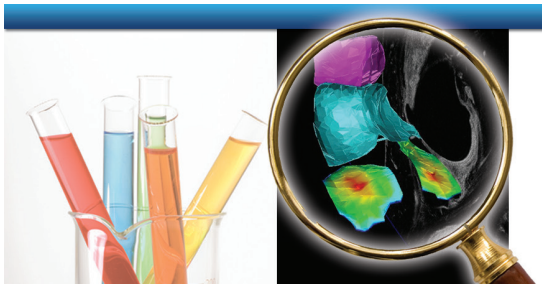
P-18 DIFFERENCES IN HIP SHAPE AMONG AFRICAN AMERICANS AND CAUCASIANS WITHOUT HIP OA USING ACTIVE SHAPE MODELING : THE JOHNSTON COUNTY OA PROJECT
A.E. Nelson[1], F. Liu[2], J.A. Lynch[2], T.A. Schwartz[1,3], N.E. Lane[4], J.M. Jordan[1]; [1]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, USA, [2]University of California at San Francisco, San Francisco, CA, USA, [3]University of North Carolina Gillings School of Global Public Health, Department of Biostatistics, Chapel Hill, NC, USA, [4]University of California Davis, Sacramento, CA, USA



POSTER INDEX

P-19 THIGH MUSCLE CROSS SECTIONAL AREAS AND STRENGTH DO NOT DISPLAY SIGNIFICANT CHANGES OVER TWO-YEARS IN EARLY OR ADVANCED PAINFUL KNEE OA

AS Ruhdorfer[1], T Dannhauer[1,2], W Wirth[1,2], M Hudelmaier[1,2], M Sattler[1], CK Kwoh[3], A Guermazi[4], DJ Hunter[5], O Benichou[6], F Eckstein[1,2], for the OAI investigators
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P-20 THE IMPACT OF MINIMUM JOINT SPACE WIDTH EXCLUSION CRITERIA ON THE SENSITIVITY TO CHANGE IN KNEE OSTEOARTHRITIS - DATA FROM THE OAI

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P-21 AUTOMATIC MULTI-ATLAS-BASED SEGMENTATION OF CARTILAGE FROM KNEE MR IMAGES ON JULY 12th – 14th in HILTON HEAD, SOUTH CAROLINA

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P-22 AN X-RAY CLASSIFICATION PROBLEM DEMONSTRATES MRI-BASED SUBREGIONAL CARTILAGE THICKNESSES PERFORM BETTER THAN AGGREGATED MEASURES

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GlaxoSmithKline, King of Prussia, PA, USA

P-23 COMPARISON OF T1RHO IMAGING AT 3 TESLA AND 7 TESLA IN KNEE CARTILAGE

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P-24 DEGENERATIVE CHANGES FIVE YEARS AFTER AN ANTERIOR CRUCIATE LIGAMENT RUPTURE ASSESSED BY MOAKS

B.L. van Meer[1], E.H.G. Oei[2], E.R.A. van Arkel[3], S.M.A. Bierma-Zeinstra[1], J.A.N. Verhaar[1], M. Reijman[1];
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P-25 THE USE OF MIXED EFFECTS MODELS IN ASSESSING SUBREGIONAL KNEE CARTILAGE THICKNESS CHANGE BETWEEN TREATMENT ARMS OF A CLINICAL TRIAL

R. J. Buck;
StatAnswers Consulting LLC, Minneapolis, MN, USA

P-26 X-RAY ACQUISTION CHALLENGS IN CLINICAL TRIALS: CHALLENGES AND SOLUTIONS POSED BY THE SYNAFLEXER™

R. McCarrie, **C.G. Miller**;
BioClinica, Inc., Newtown, PA, USA

P-27 CROSS-SECTIONAL AREA VERSUS VOLUME OF QUADRICEPS MUSCLE AND INTERMUSCULAR FAT IN WOMEN ENROLLED IN THE OAI

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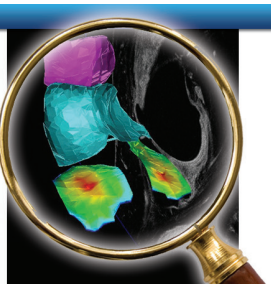

OABiomarker Global Initiative

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

POSTER INDEX

P-28 THE ASSOCIATION OF MEDIAL TIBIAL AND FEMORAL CARTILAGE MORPHOLOGY TO GAIT BIOMECHANICS IN INDIVIDIUALS WITH KNEE OSTEOARTHRITIS

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P-29 A COMPARISON OF CARTILAGE T2 MAPS GENERATED BY GE, PHILIPS AND SIEMENS

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P-30 PRELIMINARY VALIDATION OF TWO METHODS (HIMRISS, HOAMS) FOR ASSESSMENT OF MRI ABNORMALITIES IN HIP OSTEOARTHRITIS

J. Cibere[1,2], U. Weber[3], J. Jaremko[4], R.G. Lambert[4], D. Loeuille[5], V.Zubler[3], F. W. Roemer[6,7], E. C. Sayre[2], W.P. Maksymowych[8];
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P-31 OCCURRENCE AND SEVERITY OF KNEE OA IN BABOONS: A PRIMATE MODEL FOR HUMAN OA

T.E. Macrini[1], H.B. Coan[2], S.M. Levine[2], T. Lerma[1], C.D. Saks[1], D.J. Araujo[1], T.L. Bredbenner[3], R.D. Coutts[4], D.P. Nicolella[3], L.M. Havill[2];
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P-32 ASSOCIATION BETWEEN THE LOWER SERUM HOMOCYSTEIN LEVELS AND THE DOUBTFUL KNEE OSTEOARTHRITIS IN JAPANESE MEN IN EARLY FORTIES

H Kaneko[1], M Ishijima[1,2,3], L Liu[1,2], I Futami[1], R Sadatsuki[1,3], A Yusup[1,3], Y Tamura[2], R Kawamori[2], K Kaneko[1,2,3];
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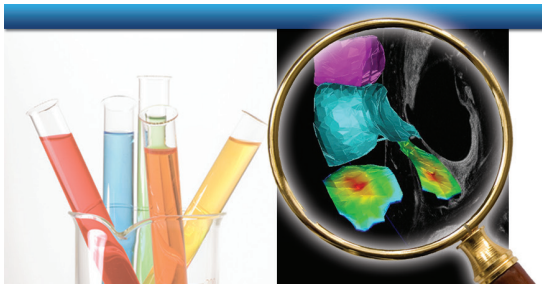

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THE ASSOCIATION BETWEEN CLINICAL OUTCOME AND CHANGE OF CARTILAGE THICKNESS AND TOTAL AREA OF SUBCHONDRAL BONE OVER TWO AND FIVE YEARs IN A TREATMENT RCT OF PATIENTS WITH ACUTE ANTERIOR CRUCIATE LIGAMENT INJURY

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INTRODUCTION: An ACL tear is a serious and common knee injury, mainly affecting young active adults. Little is known about early morphologic changes in the injured knee and we are not aware of any previous work on the relation between such changes and patient-reported outcomes in this group of patients.

OBJECTIVE: 1) To investigate the association between patient relevant outcomes and changes in cartilage thickness (ThC) and total area of subchondral bone (tAB) of the total femurotibial joint at 2 and 5 years follow-up in patients with an acute ACL injury to a previously uninjured knee, and 2) to explore these associations in subgroups of treatment actually received.

METHODS: 121 young (mean age 26.1 years) active adults with an acute ACL tear in a previously un-injured knee were included in an RCT comparing rehabilitation plus early ACL reconstruction (ACLR, n=62) and rehabilitation plus the option of having a delayed ACLR if needed (n=59). A complete set of sagittal MR images for baseline, 2, and 5 year follow-up was available for 107 of the 121 participants (57 treated with early ACLR, 25 treated with delayed ACLR and 24 treated with rehabilitation alone). Cartilage thickness (ThC) and total area of subchondral bone (tAB) were assessed by manual segmentation in the medial (MFTC) and lateral (LFTC) compartment of the femorotibial joint (FTJ) with blinding to time points. We calculated the 2 and 5 year changes of ThC and tAB of the total FTJ and compared these measures to the primary outcome of the original RCT (an average score computed from four of the five subscales of the Knee Injury and Osteoarthritis Outcome Score [$KOOS_4$]) at 2 and 5 years using the Pearson correlation coefficient.

RESULTS: No statistically significant correlations were found between the 2 and 5 year change of ThC and KOOS4 at 2 and 5 years for the full analysis set or for the treatment actually received subgroups. There was a significant correlation between the 5 year change of FTJ tAB and KOOS4 at 2 ($r=-0.2$, $p=0.04$), but not at 5 (-0.1, $p=0.38$), years in the full analysis set. This was predominantly driven by the change among those treated with early ACLR where the latter correlations were -0.29 ($p=0.03$) and -0.21 ($p=0.12$) for KOOS4 at 2 and 5 years respectively. In the early ACLR group, there were also significant correlations between the 2 year change in FTJ tAB and KOOS4 at 2 (-0.33, $p=0.01$) and 5 years (-0.27, $p=0.04$). No significant correlations were found between the 5 year change in FTJ tAB and KOOS4 in this group at 5 years (-0.21, $p=0.12$) or in those treated with delayed ACLR ($-0.19< r >0.12$, $p\geq0.35$) or rehab alone ($0.05< r >0.32$, $p\geq0.12$).

CONCLUSION: We did not find a relation between the 2 and 5 year change in cartilage thickness in the total FTJ and the clinical outcome at 2 and 5 years after acute ACL injury. However, our results indicate that increasing total areas of subchondral bone in FTJ over the first 5 years after injury may be related to a worse clinical outcome at 2 years. This may be especially true for those treated with early ACL reconstruction where increasing FTJ tABs over the first 2 years after injury were related to worse clinical outcome at both 2 and 5 years.

SPONSORS: The KANON study received funding from the Swedish Research Council, the Medical Faculty of Lund University, Region Skåne, Thelma Zoegas Fund, Stig & Ragna Gorthon Research Foundation, Swedish National Centre for Research in Sports, Crafoord foundation, Tore Nilsson research fund, and Pfizer Global Research. Image analysis was funded by NanoDiaRa (NMP4-LA-2009-228929)
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QUANTITATIVE BONE MARROW LESION CHANGES RELATE TO CARTILAGE PARAMETER CHANGES: DATA FROM THE OSTEOARTHRITIS INITIATIVE

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INTRODUCTION: Previous research has demonstrated that bone marrow lesions (BMLs), common MRI findings in osteoarthritis (OA), are related to cartilage integrity. Only one study has longitudinally evaluated quantitative 3-dimensional assessments of BML size and quantitative cartilage morphometry but it did not detect a relationship between changes in BML size and cartilage morphometry. That study, however, was a secondary analysis of a clinical trial and used an approximate measure of BML size.

OBJECTIVE: The purpose of this study was to assess the relationship between quantitative 3-dimensional assessments of BML volume and quantitative cartilage morphometry in a cohort from the OAI.

METHODS: Knees were selected from the OAI among 732 knees with cartilage segmentation results at baseline and the 24-month visit (data sets: kmri_qcart_eckstein00 [version 0.4], kmri_qcart_eckstein03 [version 3.3]). Only knees with cartilage dAB on the tibia and femur in the index compartment (defined as the tibiofemoral compartment with greater dAB) were selected (n = 196). Denuded area was assessed on the medial tibia, lateral tibia, central medial femur, and central lateral femur. The final set of 40 knees was selected to include 20 knees with a lateral tibiofemoral index compartment and 20 knees with a medial tibiofemoral index compartment. Among the 20 knees with medial or lateral index compartments, knees were selected that had the least change in femur dAB (n = 5), greatest change in femur dAB (n = 5), the least change in tibia dAB (n = 5), and greatest change in tibia dAB (n = 5). These selection criteria were intended to provide a diverse range of dAB change. BML volume was determined on sagittal intermediate-weighted, turbo spin echo, fat-suppressed MRI by one rater using a semi-automated segmentation method (ICC [3,1 model] = 0.79 to >0.99). Change over 2 years was calculated as follow-up minus baseline. Pearson correlation coefficients were performed to assess the relationship between 2-year BML volume change and 2-year cartilage morphometry change (cartilage thickness and dAB). Potential outliers were explored based on a 95% prediction ellipse. All analyses were limited to the index compartment.

RESULTS: Only 38 knees were evaluated because one knee had poor image quality and another was classified as having collapse post avascular necrosis in the index femur. The cohort was 25 (66%) females, 36 (95%) progression cohort members, 100% KLG > 1, and was on average 61 ± 8 years of age, as well as 29.9 ± 5.3 kg/m^2 body mass index. Tibia BML volume change had a positive relationship to tibia dAB change ($r = 0.33$, $p = 0.04$). One statistical outlier was identified in the tibia and verified on visual inspection by an independent investigator that did not perform the measurements. With this outlier omitted a significant negative association was detected between tibia BML volume change and tibia cartilage thickness change ($r = -0.34$, $p = 0.04$) as well as tibia BML volume change and tibia dAB change ($r = 0.42$, $p = 0.01$). There were no significant associations detected with femur BML volume.

CONCLUSION: Among participants with knee OA an increase in tibia BML volume is associated with longitudinal tibia cartilage loss. Significant associations in the tibia and not the femur may be a result of the entire tibia cartilage being assessed while only the weight-bearing region of the femur was evaluated (omitting the patellofemoral region).

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SYMMETRIC PREVALENCE OF CARTILAGE DAMAGE, BONE MARROW LESIONS AND MENISCAL LESIONS IN SUBJECTS WITH KNEE PAIN: THE JOG STUDY

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INTRODUCTION: Several risk factors for osteoarthritis (OA) have been described to be associated with an increased risk for incident radiographic OA, on a local (joint) or systemic (person) level. While radiography depicts articular changes only late in the disease process, magnetic resonance imaging (MRI) is capable of visualizing tissue pathology at a much earlier stage. Most MRI-based studies have used a one knee per person approach and thus data on bilaterality of OA features is sparse. One study described a symmetrical pattern for hand OA based on radiography [1] but there are no studies assessing bilaterality of MRI based OA-features on the knee joint.

OBJECTIVE: Study aim was to describe symmetricity of MRI-detected OA features in a cohort with knee pain.

METHODS: 169 subjects aged 35-65 with chronic, frequent knee pain were included in the Joint in Glucosamine (JOG) study. 3T MRI of both knees was performed using the same pulse sequence protocol as in the Osteoarthritis Initiative (OAI). Knees were semiquantitatively assessed according to the WORMS system by one expert MSK radiologist. Cartilage damage and bone marrow lesions (BMLs) were read in five plates (medial/lateral femur, medial lateral tibia, patella, femoral trochlea) while meniscal damage was read in three medial and three lateral subregions. Chi^2 tests were used to compare the proportion of people with unilateral tissue pathology to the proportion what would be expected if the two knees were independent. For this analysis, all MRI features were divided into present (score≥1) and absent (score=0). We further used linear weighted (w) kappa statistics to describe agreement between knees for cartilage damage and BMLs in the same articular plates using the full WORMS scores (0-4 for cartilage and 0-3 for BML).

RESULTS: 52.1 % of participants were men, mean age was 51.2 (±6.2) years old, mean BMI was 29.0 (± 4.1). The worst Kellgren/Lawrence (KL) grades in either knee were: K/L 0: 37 (21.9%) knees, K/L 1: 14 (8.3%) knees, K/L 2: 26 (15.4%) knees, K/L 3: 78 (46.2%) knees K/L 4: 14 (8.3). All plates showed a significant lower degree of unilaterality for any cartilage damage (ranging between 15.5% and 32.0%) than expected (ranging between 27.1% and 50.2%). For any BMLs the degree of unilaterality was lower for the patella, trochlea, medial tibia, and medial femur; for any meniscal damage the degree of unilaterality was lower for all medial meniscal subregions but not lateral. All plates showed higher overall % agreement (range 82.6-94.7%) than expected (range 73.0-93.1%) for cartilage damage and BMLs. Moderate agreement (defined as w-kappa 0.4-0.6) was observed for patellar and trochlear cartilage damage (0.59 and 0.54) and patellar (0.41) BMLs.

CONCLUSION: A higher degree of symmetricity of articular tissue damage than expected by chance was observed in this cohort of subjects with knee pain. These findings support the hypothesis that OA is a multifactorial disease triggered by risk factors on an individual joint level but also by person-based risk factors that predispose joints not only to radiographic OA but also to articular tissue damage commonly associated with OA.

REFERENCES: [1]Niu J, et al. Rheumatology 2003;42:343–348

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THE ASSOCIATION BETWEEN RADIOGRAPHIC HAND OSTEOARTHRITIS, MENISCAL DAMAGE, AND TORN ANTERIOR CRUCIATE LIGAMENT

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INTRODUCTION: Meniscal damage and anterior cruciate ligament (ACL) tear are risk factor for the development of knee osteoarthritis (OA). However, studies addressing potential systemic or genetic factors associated with meniscus damage and ACL tears in middle-aged elderly are sparse.

OBJECTIVE: To study whether radiographic hand OA, a possible biomarker of general OA susceptibility, is associated with meniscal damage and ACL tear.

METHODS: We studied 974 subjects (56.9% women, 92.9% Caucasians) between 50 and 90 years of age drawn via census tract data and random-digit dialing from Framingham, MA, USA. One reader assessed bilateral hand radiographs according to the Kellgren and Lawrence (KL) scale (a total of 30 joints). Other readers assessed right knee 1.5T MRI scans for meniscal integrity and ACL status. A fourth reader graded all frontal knee radiographs obtained by semi-flexed weight-bearing fixed-flexion protocol according to the KL scale. All readers were blinded to the other readings and clinical data. We divided the sample into three groups based on the number of finger joints with radiographic OA (KL grade $\geq$2). We calculated the prevalence of meniscal damage (i.e., tear or maceration/destruction in at least one subregion of either the medial and/or the lateral meniscus) and ACL tear in those with 1 to 2 and$\geq$3 OA finger joints, respectively, compared with those who had no OA in any finger joints using Poisson regression adjusting for age, sex and body mass index. We also evaluated the above associations in subjects with KL grade 0 in their right knee (n=748), i.e., excluding all knees with evidence of radiographic structural findings suggesting tibiofemoral OA (KL grade $\geq$1).

RESULTS: The proportion of subjects in the study sample (n=974) without radiographic OA in the finger joints was 35.0%, while radiographic OA in 1 to 2, and$\geq$3 finger joints was present in 27.8% and 37.2%, respectively. The prevalence of a meniscal damage in one or more locations on MRI of the right knee according to number of finger joints with OA (grouping as above) was 24.9%, 31.7%, and 47.2%, respectively. The corresponding proportions for ACL tear was 3.0%, 3.0%, and 5.0%, respectively. The adjusted odds of having meniscal damage was significantly increased with 3 or more finger joints affected by radiographic OA, these associations remained similar in knees with KL grade 0 (n=748, Table). There was no statistically significant association between hand OA and ACL tear (data not shown).

TABLE: The association between radiographic hand osteoarthritis and right knee meniscus lesions on MRI. PR= prevalence ratio

	Whole study sample (n=974)		No evidence of radiographic knee osteoarthritis (n=748)	
Number of hand joint groups* with osteoarthritis	Crude PR	Adjusted PR* (95% CI)	Crude PR	Adjusted PR* (95% CI)
none	Reference category		Reference category	
1	1.23	1.08 (0.84 to 1.40)	1.06	1.10 (0.69 to 1.39)
2	1.66	1.28 (0.99 to 1.66)	1.52	1.28 (0.89 to 1.83)
3 or more	2.15	1.54 (1.20 to 1.99)	1.93	1.54 (1.05 to 2.26)

**Adjusted for age, sex, and body mass index.*

CONCLUSION: Presence of multiple finger joints with radiographic OA is associated with meniscal damage of the knee. The results suggest a common systemic/genetic predisposition and (or) a common environmental risk factor for radiographic hand OA and meniscal damage in the middle-aged and elderly.

DICLOSURE STATEMENT: AG is shareholder of Boston Imaging Core Lab, LLC (BICL), Boston, Massachusetts, USA, a company providing radiological image assessment services, and consultant to Merck Serono, Novartis, Genzyme, AstraZeneca, and Stryker. FWR is shareholder of BICL and consultant to Merck Serono and NIH.
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THE ABILITY OF BIOCHEMICAL MARKERS TO REFLECT (VERY) EARLY RADIOGRAPHIC KNEE AND HIP OSTEOARTHRITIS: DATA FROM CHECK, A COHORT OF EARLY OSTEOARTHRITIS.

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INTRODUCTION: Having valid biochemical markers (biomarkers) for osteoarthritis (OA) would be a valuable contribution to clinical practice, trials of potential therapeutic agents, and/or identification of therapeutic targets. To be of optimal value in these contexts biomarkers would especially need to reflect OA burden and progression in early-stage rather than end-stage OA.

OBJECTIVE: To determine to what extent systemic biomarkers reflect present and future radiographic early-stage knee and hip OA.

METHODS: CHECK (Cohort Hip & Cohort Knee) is a running 10-year prospective study of 1002 participants, aged 45-65 years, with complaints of pain and/or stiffness of knee(s) and/or hip(s) that had never or not longer than 6 months ago visited the general practitioner for these symptoms for the first time.
Baseline serum and urinary biomarkers of cartilage (uCTX-II, sCOMP, sPIIANP, sCS846), bone (uCTX-I, uNTX-I, sPINP, sOC) and synovial metabolism (sHA, sPIIINP) were assessed by ELISA or RIA.
Knee and hip radiographs were obtained at baseline and after 2 and 5 years. OA burden was expressed as the summed Kellgren & Lawrence (K&L) grade for hips and knees at baseline. OA progression was expressed as the area under the curve (AUC) of summed K&L grades during 5 years.
Associations of biomarkers with OA burden and progression were investigated by linear regression. Biomarkers were used individually as well as in sum and dissociation scores (as standardized Z-scores). Sum scores were aimed to reflect metabolism in total (i.e. synthesis and degradation), while dissociation scores were meant to describe the dissociation between synthesis and degradation (i.e. catabolism or anabolism).

RESULTS: Data were complete for 800 participants at baseline and 725 participants at all time points.
Associations with baseline summed K&L grade were observed for uCTX-II, sCOMP, sPIIANP, sHA, and sPIIINP (max stand beta=0.183, P<0.001 for sHA), and persisted to a lesser extent for uCTX-II and sHA after adjustment for age, gender, and BMI (max stand beta=0.129, P<0.001 for uCTX-II).
The AUC of the summed K&L grades was associated with uCTX-II, sCOMP, sPIIANP, and sCS846 (max stand beta =0.133, P<0.001), and persisted only for sCOMP after adjustment for demographics and baseline summed K&L grade (stand beta=0.105, P=0.005).
Only summed cartilage marker scores were associated somewhat stronger with baseline summed K&L grade as compared to their individual components (uCTX-II+sCOMP+sPIIANP+sCS846: stand beta=0.195, P<0.001).
Stronger associations with the AUC of summed K&L grades as compared to their individual components were observed for cartilage sum scores (uCTX-II+sCOMP+sPIIANP+sCS846: stand beta=0.201, P<0.001) and synovial sum and dissociation scores (sHA+sPIIINP and sHA-sPIIINP: stand beta=0.096, P=0.01).

CONCLUSION: Associations with burden and progression of (very) early hip and/or knee OA were especially observed for cartilage and synovial biomarkers. Combining biomarkers in sum and dissociation scores did increase these associations only to a limited extent.
Associations were too weak to be of clinical utility. The low grade of the associations may be due not only to limitations of systemic biomarkers but also radiography in reflecting OA, especially in early-stage disease. Nevertheless, together with literature data these results indicate that the search for biomarkers for (very) early OA should be primarily aimed at (combinations of) cartilage and synovial metabolism.

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COLLAGEN BIOMARKER RESPONSE TO ACUTE JOINT INJURY IN A NON-TERMINAL ANIMAL MODEL OF OSTEOARTHRITIS

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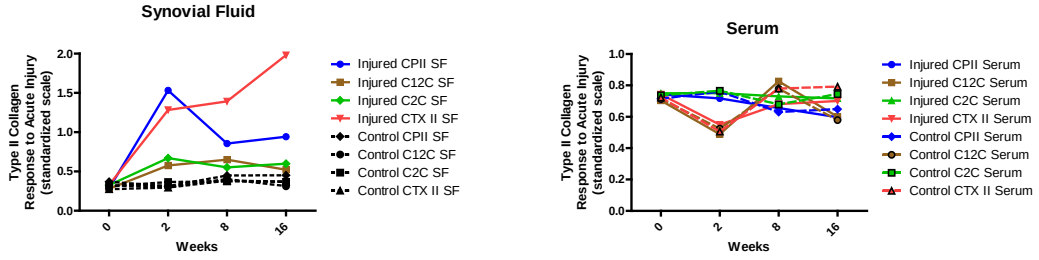
INTRODUCTION: Biomarkers of cartilage metabolism have potential to identify changes immediately after joint injury and in response to onset and progression of OA. Identifying longitudinal changes in type II collagen metabolism after injury may facilitate earlier diagnosis and understanding about disease onset.

OBJECTIVE: We hypothesized that collagen biomarkers in synovial fluid (SF) and serum would identify early metabolic changes that occur after acute osteochondral (OC) injury which may progress toward OA.

METHODS: Twenty-two clinically and radiographically normal age- and sex-matched Quarter Horses were randomly divided into 2 groups: (1) horses (n=11) that had an OC fragment created arthroscopically on the dorsomedial aspect of the first phalanx in one randomly selected metacarpophalangeal (MCP) joint and a sham operation in the contralateral joint at week 0; and (2) unoperated exercise control horses (n=11). All horses were exercised on a high-speed treadmill 5 days/week from week 2 to week 16. Blood was collected from the jugular vein and SF samples were collected without lavage from both MCP joints of all horses at baseline (week 0), week 2, 8, and 16. Collagen degradation (CTXII [IDS/Nordic], C2C, C12C [IBEX]) and synthesis (CPII [IBEX]) ELISA assays were used to analyze SF and serum samples. All assays were previously validated for equine use. Data were assessed for normality and outliers removed from further analyses. A repeated measures ANOVA with a Tukey's test for multiple comparisons was used. $P \leq 0.05$ was considered significant. Procedures were approved by animal care committees.

RESULTS: In SF, all collagen biomarkers significantly increased from baseline at weeks 2, 8, and 16 ($P<0.0001$). In addition, SF from OC injured joints had significantly higher concentrations of all collagen biomarkers when compared to SF from control and sham joints ($P<0.05$). The only exception was at week 8 with CPII, when OC injured and sham joints were not significantly different. In the figures below, all of the collagen biomarkers are compared on a standardized scale to show the relative response over time. The only significant change in serum biomarkers was a decreased C12C concentration at week 2 in both OC injured and control horses ($P<0.05$). There were no significant differences in serum concentrations between OC injured horses and controls.



CONCLUSIONS: This study demonstrated that in an acute joint injury model of OA, SF is more sensitive than serum in determining collagen biomarkers changes. C12C and C2C were elevated throughout most of the study period, but started to decline with chronicity. Since these neoepitopes result from collagenase cleavage, this may suggest that most of the collagenase damage to collagen occurs within the first 2 to 3 months of injury. Conversely, CTX II increased throughout, suggesting that telopeptide breakdown is mediated by other biochemical pathways. Collagen synthesis increased by week 2 after injury, but came back toward baseline by week 8 while degradation (CTX II) increased. This may suggest that in spite of an early anabolic response in the injured joint, it becomes more catabolic between weeks 2 and 8 after injury.

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GWAS of Osteoarthritis Biomarkers Serum Hyaluronic Acid and Cartilage Oligomeric Matrix Protein Implicates FOXN4, ETV6, KIAA1217, ZNF521, SPHKAP, and CSGALNACT1

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INTRODUCTION: Increases in OA prevalence and severity have not been accompanied by the advances in our knowledge of OA pathogenesis that are needed to effectively prevent and treat this complex disease. The identification of genetic factors with the potential to affect disease progression and etiology could lead to rapid and significant progress in OA research.

OBJECTIVE: Our objective is to identify genomic regions potentially associated with OA disease risk and/or progression through a genome-wide association study (GWAS) of serum HA and COMP in a family-based cohort study with more power to identify rare genetic variants then commonly used case control studies.

METHODS: Biomarkers were measured using stored serum samples from San Antonio Family Study (SAFS) participants. All participants gave informed consent and the study was approved by the Institutional Review Board. HA and COMP levels were assessed via ELISA (Corgenix and BioVendor R&D) in 935 (HA) and 933 (COMP) members of large extended families. We used existing data for 1,000,000 SNPs and the software package SOLAR to test for association between quantitative variation in circulating concentrations of HA and COMP and specific SNP variants. Highly significant SNPs were evaluated for details regarding SNP location; whether the SNP was intergenic, intronic, exonic or noncoding; if the SNP was upstream or downstream of a gene; whether the SNP is in a conserved region of the genome; genes in close proximity to the SNP and genes identified in other studies as being associated with the SNP (expression quantitative trait loci; eQTLs using bioinformatics resources dbSNP, SNP SCAN, and Pupasuite 3. Genes in close proximity to a SNP, or associated with the SNP through eQTL studies, were prioritized for further evaluation of potential involvement in OA etiology and pathogenesis.

RESULTS: Many of the most strongly associated SNPs ($p=4x10^{-7}$ to $7.8x10^{-6}$) showed a unifying theme of relevance to development of cartilage and the skeletal system. HA GWAS revealed 1) three SNPs implicating FOXN4, a member of the singed helix/forkhead transcription factor family whose members are important to embryonic skeletal system development, 2) rs16907395, located within ETV6 that associates with osteochondrogenic transcription factor RNX1, 3) rs6482369, an eQTL for TMEM198 – a membrane protein required for Wnt signaling which is critical to bone and cartilage formation – and which is located within the KIAA1217 gene, a human homolog of the mouse skt gene which is important in mouse embryonic skeletal patterning. COMP GWAS revealed 1) three SNPs implicating ZNF521, a transcription factor involved in regulating osteoblast commitment and differentiation, 2) three SNPs near CSGALNACT1 which is critical to chondroitin sulfate biosynthesis and aggrecan formation in cartilage.

CONCLUSION: We identify novel genomic regions potentially involved in OA disease progression as an important step in identifying genetic factors potentially involved in OA. Many of the most strongly associated SNPs showed a unifying theme of relevance to skeletal system and cartilage development which may implicate a broad spectrum of skeletal development signalling processes in OA. Our next step is to obtain image data to complement the biomarker and comprehensive genetic data in the SAFS population.

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BIOPSIES AND IMAGING AT ACL RECONSTRUCTION

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INTRODUCTION: The ability to relate noninvasive measures of whole joint condition and cartilage composition to direct measures of cartilage changes in the acute phase of joint injuries increases the likelihood of successful intervention.

OBJECTIVE: Obtain direct physical measures of cartilage PG distribution measured by MRI and serum biomarkers as they relate to cartilage condition two-four weeks after osteochondral injury.

METHODS: Eight osteochondral biopsies from the femoral trochlea were obtained at ACL reconstructive surgery. The average age of these acute ACL-rupture patients was 23 years old at the time of injury (18.8-29.9yo) and the time from injury to ACLR was 41 days (12-81). The 3.5mm diameter cylindrical specimens were imaged in a Varian 4.7T, 38mm diameter coil. Fast spin echo-based pulse sequence, TR/TE = 3000/12 ms, echo train length (ETL = 8) and in-plane resolution of 0.1x0.2mm with 1mm slice thickness were used with T1rho spinlock times of 5, 10, 20, 30, 40, 60, and 80ms. Cryo-embedded cartilage was cut into 5micron thick sections and stained with Safranin-O, Fast-Green and Weigert's for histological analysis. The directly apposed portion of the cartilage was assayed for proteoglycan content (μg/μl). Automated Mankin scoring [JOR 2009;27:522-] was used to extract Safranin-O red hue distribution within four cartilage zones, which were mapped directly onto the T1rho images to extract complementary MRI relaxation times. Serum samples were also acquired. ELISA assays were performed for markers of bone turnover including bone sialoprotein (BSP), Bone alkaline phosphatase (BAP), osteoclastic tartrate resistant alkaline phosphatase (TRAP5b), the type II collagen degradation marker C2C, and the osteoarthritis marker chondroitin sulfate epitope 3B3 (CS3B3).

RESULTS: Table 1. Osteochondral PG and T1rho values are presented across four cartilage zones.

	Mankin Percentage Distribution			T1rho Relaxation Time (ms)	
ROI	Avg	Std	Based on 24.4 mg/ul PG Avg	Avg	Std
Superficial	$7.1x10^{-03}$	$3.0x10^{-2}$	$1.7x10^{-3}$	101.1	29
Transitional	24.0%	16.2%	5.9	90.3	25.7
Radial	68.9%	11.7%	16.8	81.4	21.6
Deep	7.1%	5.4%	1.7	70	19.1
In Vitro Full Cartilage	-	-	24.4 (5.9)	85.7	29.1
In Vivo Full Cartilage	-	-	-	58.0	19.5

Table 2. Serum Biomarkers results from patients with ACL rupture (ACL) or tibial plafond fracture (IAF) measured 2-4 weeks after injury.

Marker	Units	ACL			IAF			Significance (t-test)
		mean	std dev	n	mean	std dev	n	
C2C	ng/mg	705	99.2	4	1560	760	13	P = 0.045.
BSP	ng/mg	84.1	31.0	4	47.6	31.1	12	P = 0.061
BAP	μg/mg	0.095	0.021	4	0.074	0.035	13	P = 0.283
3B3	ng/mg	28.4	8.48	4	4.41	5.05	13	P < 0.001
TRAP	mU/mg	1.30	1.84	4	18.8	7.25	12	P < 0.001

CONCLUSION: T1rho results of the osteochondral specimens were elevated from normal. At 2-4 weeks post injury, there were significant differences in serum biomarkers in blunt trauma injured ACL and IAF patients. TRAP and C2C were significantly higher in IAF patients, a finding consistent with bone and cartilage turnover expected during fracture healing. CS3B3 was significantly higher in ACL patients, consistent with early osteoarthritic changes. The relationships of these imaging and biomarker data are inconclusive, but continued complementary sample collection and recommendations of this workshop should enhance that search.

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ASSOCIATION OF MR RELAXATION TIMES WITH MUSCLE MORPHOLOGY AND FUNCTIONAL LOADING AT THE KNEE

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INTRODUCTION: Muscle strengthening and interventions to lower knee adduction moment (KAM) are commonly used to alter loading patterns in an attempt to slow the pathogenesis of knee OA. It needs to be seen if T1rho and T2 MR relaxation times, which are sensitive to early biochemical changes seen in knee OA, are related to these mechanical risk factors to allow their use in prognostic and interventional studies.

OBJECTIVE: To analyze the relationship of articular and meniscal cartilage composition T1ρ and T2 relaxation times with (1) static and dynamic knee alignment, (2) functional knee loads during walking and, (3) thigh muscle cross-sectional area (CSA), in young healthy subjects.

METHODS: 33 young healthy (49 knees), pain free, active subjects (20-35 years, BMI < 28 kg/m^2) completed 3-T MRI scans of the knee and 3-D motion capture while walking. High resolution MR sequences were used for quantification of ThC (Sagittal SPGR - TR/TE = 15/6.7 ms, flip angle = 18, FOV = 14 cm, matrix = 512 x 512, slice thickness = 1 mm, bandwidth = 31.25 kHz, NEX = 1), T1rho - and T2 relaxation times (Sagittal TSL = 0/10/40/80 ms, prep TE = 0/13.7/27.3/54.7 ms, FOV = 14 cm, matrix = 256 x 128, time of recovery = 1.2 sec, slice thickness = 4 mm) for articular and meniscal cartilage, and quadriceps (Q)and hamstrings (H) muscle cross-sectional area (CSA) (Midthigh Axial - TE/TR = 6.41/800, slice thickness = 10 mm, matrix = 384 x 1932, ETL = 2, bandwidth = 150 kHz, NEX = 4). Frontal plane kinematics and kinetics during stance phase of walking were calculated using standard 3-D motion capture techniques. Long limb radiographs were available from 27 knees for assessment of static alignment. Multiple linear regression models accounting for age, BMI and walking speed were used to identify loading and muscle parameters which predicted ThC, T1rho and T2 parameters.

RESULTS: **(1)** Greater valgus was associated with higher lateral T2 (r = 0.489, p = 0.010) and greater varus was associated with greater medio-lateral T2 ratio (r = -0.395, p = 0.042) of articular cartilage . **(2)** KAM impulse explained 12.8 % of the variance in medio-lateral ratio (p = 0.025) of ThC. Peak sagittal moment was found to explain 50.6% of the variance in the FT T1rho and T2(p < 0.001) for articular cartilage. Peak KAM predicted medio-lateral T1rho ratio (R^2 = 0.245, p = 0.001) of meniscus. **(3)** Q:H muscle ratio predicted FT T1rho(R^2 = 0.107, p = 0.035). Age, gender and Q:H predicted FT T2(R^2 = 0.353, p = 0.001). Medio-lateral quadriceps CSA predicted T1rho times for medial meniscus (R^2 = 0.146, p = 0.012), and medio -lateral ratio(R^2 = 0.114, p = 0.029). Q:H and medio-lateral quadriceps ratio explained 45.7% of the variability in KAM impulse (p < 0.001) and 48% of the variability in peak KAM (p < 0.001). For 1st peak KAM, it was only Q:H CSA ratio that was found to predict 36.4 % of the variability (p < 0.001) and also for frontal rate of loading (R2 = 0.289, p < 0.001).

CONCLUSION: Data show that T1rho and T2 relaxation times are sensitive to static and dynamic mechanical loading and could be used in interventional and clinical studies. Malalignment and KAM are associated with initial medio-lateral imbalances of cartilage composition which could progress to OA. The impact loading is more pronounced on the meniscus than articular cartilage indicating a more important role of meniscus in pathogenesis of knee OA than previously thought. Finally, these data support the importance of targeted muscle balance training in addition to strengthening since muscle imbalance is related to walking patterns known to predispose to OA as well as higher MR relaxation times for articular and meniscal cartilage. We continue to process the data to assess relationship of functional mechanics with sub-regional articular cartilage laminar T1ρ- and T2 relaxation times and texture values.

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ACUTE ANTERIOR CRUCIATE LIGAMENT INJURY CAUSES CARTILAGE THICKNESS INCREASE OVER TWO AND FIVE YEARS

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INTRODUCTION: An ACL tear is a serious and common knee injury, mainly affecting young active adults. In the long term, the risk of OA development in the injured joint is increased but little is known about structural cartilage changes in the early phase.

OBJECTIVES: Using MRI, to (1) describe the rate of change in femorotibial cartilage thickness over two and over five years after an ACL injury, and (2) determine the number of knees showing a significant increase or decrease in cartilage thickness over 2 and/or 5 years.

METHODS: 121 young (mean age 26.1 years) active adults with an acute ACL tear in a previously un-injured knee were included in an RCT comparing rehabilitation plus early ACL reconstruction (n=62) and rehabilitation plus the option of having a delayed ACL reconstruction if needed (n=59). A complete set of sagittal MR images for baseline, 2, and 5 year follow-up was available for 107 of the 121 participants. Cartilage thickness (ThC) was assessed by manual segmentation of the cartilage surfaces in the medial (MFTC) and lateral (LFTC) compartment of the femorotibial joint (FTJ) with blinding to time points. The progression definition for significant increase or decrease in ThC was based on 95% confidence intervals computed from one-year changes observed in the non-exposed reference cohort of the OAI. The thresholds were 153µm/ 149µm/ 289µm for increase and -161µm/-143µm/-256µm for decrease in ThC of MFTC/LFTC/FTJ respectively. MRI results were not unblinded for treatment group in this first step and thus we present the results for the entire sample of acutely ACL injured knees.

RESULTS: In the total FTJ, average ThC slightly increased over 2 (+0.7 % [95% CI: 0.0/+1.4 %]; paired t-test p=0.046) and 5 years (+1.9 % [+1.0/+2.8 %]; p<0.001). This change was predominantly driven by changes in the medial femorotibial compartment (+1.3 % [+0.4/+2.1 %]/ +3.1 % [+2.1/+4.1 %] over 2/5 years; p=0.003/p<0.001) whereas the average change in ThC in the lateral compartment was +0.2 % [-0.6/+1.0 %] over 2 and +0.8 % [-0.2/+1.9 %] over 5 years (p=0.58 and 0.12 respectively). Except for the posterior subregion of the LT, which showed a decrease in ThC of -4.2 % (2 year) and -4.7% (5 years), changes in subregions were close to zero or showed an increase in ThC of up to 4.7% (external subregion of cMF, 5 years). Over 2 years, 13% of the knees a showed significant decrease in the FTJ (6% in MFTC, 19% in LFTC) and 21% showed significant increase in the FTJ (26% in MFTC; 22% in LFTC). Over 5 years, the percentage of knees showing significant decrease in ThC was similar to the percentage observed over 2 years (12% in FTJ; 4% in MFTC, 18% in MFTC), whereas the percentage of knees showing significant increase in ThC was higher (30% in FTJ, 35% in MFTC, and 31% in LFTC).

CONCLUSION: A significant decrease in cartilage thickness was predominantly observed in the lateral femorotibial compartment in this post-traumatic ACL insufficiency cohort and this decrease was not more frequent after 5 than after 2 years. In contrast, a significant increase in cartilage thickness was observed with similar frequencies in both the medial and the lateral compartment and the proportion of knees showing an increase in cartilage thickness further increased between year 2 and year 5. When compared to knees with established radiographic OA, which typically show a loss in cartilage thickness, knees after a rupture of the ACL showed a slight increase of cartilage thickness on average and almost 1/3 of knees showed a significant increase in total joint cartilage thickness over the first 5 years after the injury.

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SUSCEPTIBIILTY ARTIFACTS IN THE TIBIO-FEMORAL JOINT SPACE ON 3T KNEE MRI: FREQUENCY, LONGITUDINAL FOLLOW-UP AND THEIR RELATION TO MENISCAL TEARS, RADIOGRAPHIC JOINT SPACE NARROWING AND CALCIFICATIONS

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INTRODUCTION: Linear or punctate hypointensities are commonly seen on gradient echo (GRE) sequences in the tibio-femoral joint (TFJ) space of OA joints. These are known as susceptibility artifacts (SAs) and are thought to represent vacuum phenomenon, a common radiologic finding in OA joints and vertebral disks. They appear adjacent to the cartilage or menisci, and cartilage assessment may potentially be impaired due to signal loss or be misinterpreted as a lesion.

OBJECTIVE: Aim was to assess the frequency of SAs in the TFJ space on a dual-echo steady state (DESS, - a GRE sequence very sensitive to magnetic susceptibility) and on an intermediate-weighted (IW) fat-suppressed (fs) sequence, and assess associations with intraarticular calcifications and joint space narrowing (JSN) on X-ray (XR), and with MRI-detected meniscal damage in the medial and lateral TFJ.

METHODS: 346 knees of 177 subjects aged 35-65 with knee pain were included. 3T MRI was performed at baseline and at 6-month follow-up (f/u). Baseline anteroposterior knee XR were read for JSN according to the OARSI atlas and linear/punctate calcifications within the TFJ were recorded. The WORMS system was used to assess meniscal damage on MRI, and the presence of any damage (grade $\geq$1) was recorded at baseline. Linear/punctate hypointensities representing SAs in the TFJ space were assessed on coronal DESS and IW fs sequences. All assessments were performed blinded and in a random order. XR, DESS and IW images were each read on separate reading sessions >2 weeks apart. Kappa statistics were applied to assess concordance between findings on the baseline DESS and IW fs or XR.

RESULTS: Subjects had a mean age of 52 (SD±6) years, BMI of 29±4, and 95 (54%) were men. Baseline Kellgren/Lawrence grades (for worst knee) were: K/L 0- 37 (21%) knees; K/L 1- 14 (8%) knees; K/L 2- 26 (15%) knees; K/L 3- 81 (46%) knees; and K/L 4- 19 (11%). On XR, 44 (13%) and 9 (3%) knees had medial and lateral JSN, respectively; and 7 (2%) and 14 (4%) knees had calcifications in the medial and lateral TFJ space, respectively. On MRI, 126 (36%) knees had medial and 31 (9%) knees had lateral meniscal damage. In the medial TFJ, 13 and 4 knees showed SAs at baseline on DESS and IW fs, respectively. On DESS, 6 of 13 knees had persistent SA at f/u and 6 knees had incident SA at f/u. In the lateral TFJ, 5 and 1 knees showed SAs at baseline on DESS and IW fs, respectively. On DESS, 2 of 5 knees had persistent SAs at f/u and 1 new SA was noted at f/u. In the medial TFJ, compared to knees without SAs on DESS, knees with SAs were more likely to have medial meniscal damage (9/13, 69% vs. 117/333, 35%, p=0.017) and medial JSN (5/13, 38%, vs. 39/333, 60%, p=0.016). Agreement between DESS and IW was κ=0.46 (95%CI 0.17-0.75) and that between DESS and XR was κ=0.18 (-0.06 - 0.42) in the medial TFJ. We could not calculate p-values or κ in the lateral TFJ due to a very small number of SAs.

CONCLUSION: SAs on GRE sequence in the TFJ were seen in <5% of knees in this cohort of subjects with knee pain and a spectrum of radiographic OA severity. These artifacts are more frequently observed in knees with medial meniscal tears and medial JSN, which suggests an association with more advanced OA-related joint damage. MRI-detected artifacts rarely correspond to XR-detected calcifications and commonly show longitudinal changes, which support the hypothesis that these present vacuum phenomenon.

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RESPONSIVENESS OF QUALITATIVE AND QUANTITATIVE MRI MEASURES OVER 2.7 YEARS

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INTRODUCTION: Radiography remains the only approved method to assess structural change in clinical OA trials. In order to have MRI accepted as a measurement tool in clinical trials, responsive outcome measures for structural rate of change using MRI are needed.

OBJECTIVE: The aim of this study was to compare the responsiveness of MRI-derived measures over 2.7 years.

METHODS: A total of 430 community-dwelling older adults (mean age 63.0 years, range 51 – 79 years; 51% female) were measured at baseline and approximately 2.7 years later. 1.5 T MRI scans of the right knee were performed at both time points. Tibial and femoral knee cartilage volume, tibial and femoral cartilage defects (range, 0-4), meniscal pathology and tibial bone size were determined using T1-weighted fat-suppressed (3D) gradient-recalled acquisition in the steady state. Tibial and femoral BM lesions were determined using a T2-weighted fat-suppressed 2D fast spin-echo sequence by measuring the maximum area of the lesion (mm^2). BM lesions were also scored using an ordinal scoring system (range, 0-3). Summary scores were calculated for cartilage volume, cartilage defects, and BM lesions as the sum of tibial and femoral measures. Standardized response mean (SRM) between the 2 visits for each MRI measure was calculated as the mean of change divided by the standard deviation of change.

RESULTS: The SRM for tibial and femoral cartilage volume measures ranged from -0.48 to -0.54. The best cartilage volume SRM was for total tibiofemoral cartilage volume (summary score) (-0.80). The SRM for tibial and femoral cartilage defect measures ranged from 0.33 to 0.49. The SRM for total tibiofemoral cartilage defects (summary score) was 0.62. For the meniscal pathology score the SRM was 0.59. The SRM for tibial bone area was low at -0.09. For the quantitative BM lesion measure, the SRM was 0.01 to 0.11 for tibial and femoral measures, and 0.12 for the summary measure. Using the ordinal scoring system for BM lesions the SRMs were similar (0.03 to 0.17).

CONCLUSION: These results suggest that the best sensitivity to change is seen with summary scores rather than compartment based scores. This study also demonstrates that if we relied solely on SRMs to optimize trial design, then cartilage volume would be the best outcome measure. However, in a recent clinical trial, we saw significant improvements in BM lesion size (measured quantitatively), despite low SRM values for the quantitative BM lesion measure. This was primarily due to a very large effect (around 40% in the treatment group improved). In comparison, when cartilage volume is used as an outcome in clinical trials, studies have powered on an expected 1-2% improvement in cartilage volume loss. Therefore, although one can optimize trial efficiency by finding more responsive endpoints, magnitude of effect appears equally important in selecting outcome measures.

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QUADRICEPS MUSCLE AND INTERMUSCULAR FAT VOLUME IN THE THIGHS OF MEN IN THE OAI ARE ASSOCIATED WITH PHYSICAL FUNCTION AND KNEE PAIN

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INTRODUCTION: Muscle weakness and obesity play an important role in knee OA, both in terms of incident and progressive disease. Fat and muscle tissue can be quantified by segmenting CT or MRI scans to yield measures of cross-sectional area or volume. However, the clinical relevance of these tissue measurements has not been explored. Specifically, associations between muscle and fat volumes and physical function, performance and pain in osteoarthritic individuals remain unresolved.

OBJECTIVE: To investigate the association between QM and IMF volume in the mid-thigh and physical performance/function and pain in men participating in the OAI.

METHODS: A sample of 72 men ≥50y old in the OAI database who had baseline and 2y thigh MRI scans available were randomly selected from a sub-cohort who i) had baseline and 2-year Kellgren-Lawrence (K-L) grades available, ii) had matching pixel spacing and iii) had adequately matched baseline and 2-year images. Thigh MRI scans acquired from a 7.5cm region of interest (15 slices, 5mm slice thickness) beginning 10 cm proximal to the distal femoral epiphysis were segmented using SliceOmatic 4.3 (Tomovision, QC, Canada). QM and IMF volumes were determined from the analyses of the 12 most proximal matching slices. For these analyses, only baseline volume data for the right thigh were used. Physical function/performance outcomes included WOMAC physical function and total scores, KOOS Function in Sports and Recreation score, maximum extensor force and 20 m walk time. WOMAC pain was used as the symptom outcome. Baseline data were downloaded from the online OAI database. Backwards linear regression analyses were performed to determine the association between tissue volumes and self-reported physical performance and physical function and knee pain. IMF and QM volume were both entered into each regression model together with covariates age, BMI and K-L grade.

RESULTS: The mean±SD age and BMI were 63.6 ± 8.1 years and 29.8 ± 4.1 kg/m^2, respectively. The distribution of K-L grades was: K-L 0=28, K-L 1=12, K-L 2=15, K-L 3=11, and K-L 4=6. Table 1 reports associations between tissue volumes and physical performance/function outcomes and pain. Of note is that none of the covariates were significant in the regression analyses.

Model	R	Adjusted R	Standardized β	p
KOOS Function in Sports & Recreation	0.549	0.301		
IMF	0.287	0.068	-0.330	0.030
WOMAC Pain	0.359	0.129		
QM			-0.215	0.059
IMF			0.293	0.011
WOMAC Function				
IMF			0.401	<0.001
MAX Extensor Force				
QM			0.650	<0.001
20 metre walk time				
IMF			0.290	0.013

CONCLUSION: IMF volume appears to be associated with physical function/performance outcomes to a greater degree than QM volume. These results are consistent with similar analyses conducted in women in the OAI. In fact, QM volume was only significantly associated with maximum extensor force of the corresponding leg. Men with more IMF appear to have more pain and lower levels of physical function/performance than those with less IMF. Future studies will analyze the clinical relevance of changes in tissue volume over time in this osteoarthritic population.

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A 2-YEAR RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF ORAL SELECTIVE INOS INHIBITOR, CINDUNISTAT, IN PATIENTS WITH SYMPTOMATIC OSTEOARTHRITIS OF THE KNEE

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INTRODUCTION: To date, no therapy is currently approved as a DMOAD and major efforts. The aim of this proof-of-concept study was to evaluate whether inhibition of iNOS slows the progression of knee OA. iNOS is considered an attractive molecular target since it has the potential to affect mechanisms that contribute to both structural deterioration and inflammation, not only in the articular cartilage, but also in other joint tissues such as meniscus, bone and synovium.

OBJECTIVE: To determine whether inhibition of inducible nitric oxide synthase (iNOS) using the selective iNOS inhibitor cindunistat (SD-6010), can slow progression of knee osteoarthritis (OA).

METHODS: This 2-year multinational, multicenter, double-blind, parallel group trial enrolled subjects with symptomatic knee OA. 1457 subjects were randomly assigned to once daily cindunistat (50 mg or 200 mg), or placebo. Eligible subjects had body mass index (BMI) $\geq$25 and $\leq$ 40 kg/m^2 and Kellgren and Lawrence Grade 2 or 3 in the study knee. Randomization was stratified by KLG. Radiographs were acquired using the modified Lyon-schuss protocol at baseline, 48 and 96 weeks for assessing the primary endpoint of JSN. Clinical benefit was recorded at weeks 12 and 24 and every 24 Weeks thereafter. Acetaminophen, NSAIDs and/or weak opioids were permitted. The primary analysis of the rate of JSN used a continuous time random coefficients MMRM model. The slope over the entire 96 week period was used to assess the rate of change in JSW.

RESULTS: Of 1457 randomized subjects (cindunistat 50mg, n=485; cindunistat 200mg, n=486; placebo, n=486), 1048 (71.9%) completed the study. Subjects were predominantly female (76.5%) with mean age 61.0 years and mean BMI of 31.8 kg/m^2. Fifty-six percent had KLG3. The primary analysis did not demonstrate the superiority of cindunistat in either treatment group over placebo. In an exploratory discrete time analysis of KLG2 subjects, the loss of JSW after 48 weeks was clinically significantly smaller with cindunistat (50 mg or 200 mg) than placebo. Least squares (LS) mean ± standard error (SE) losses in JSW for cindunistat 50mg (–0.048 ± 0.028 mm) and 200mg (–0.062 ± 0.028 mm) were 59.9% (95% CI: 6.8%, 106.9%) and 48.7% (95% CI: -8.4%, 93.9%) of placebo (–0.120 ± 0.028 mm; *P*=0.032 and *P*=0.081, respectively). After 96 weeks, the LS-mean losses in JSW for cindunistat 50mg (–0.132±0.036 mm) and 200mg (–0.156±0.037 mm) were 20.9% (95% CI: -50.5%, 64.0%) and 6.8% (95% CI: -72.7%, 51.7%) of the LS-mean JSW loss in the placebo group (–0.167±0.036 mm) (*P*=0.460 and *P*=0.812, respectively). In a similar analysis of KLG3 subjects, no improvement in JSN was observed. Although cindunistat showed no efficacy with respect to improvement in joint pain or function, it was generally safe and well tolerated in this population.

CONCLUSION: During the first 48 weeks of treatment, subjects with mild OA who were treated with an iNOS inhibitor had less joint space narrowing; however, this improvement was not sustained at 96 weeks. iNOS inhibition did not slow OA progression in subjects with more severe radiographic OA or in the population as a whole.

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EFFECT OF iNOS INHIBITION ON STRUCTURAL PROGRESSION OF KNEE OA OVER 2 YEARS – DEFINED AS MRI-BASED QUANTITATIVE CARTILAGE THICKNESS CHANGE

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INTRODUCTION: Current treatment for knee osteoarthritis is mainly focused on controlling symptoms and replacing damaged joints, and no interventions have yet been approved for modifying the course of the disease at a structural level. In the absence of disease modifying drugs (DMOADs), knee replacements are projected to increase to over 3 million annually in the US by 2030. Effective DMOAD treatment to control structural progression and symptoms in (knee) OA is hence desperately needed.

OBJECTIVE: To determine whether inhibition of inducible nitric oxide synthase (iNOS) can slow structural progression of knee osteoarthritis (OA), defined as longitudinal cartilage thickness change (ΔThCtAB) over 6, 12, and 24 months (M) assessed using quantitative MRI.

METHODS: The main study was a 2-year, multinational, multicenter, double-blind, parallel group DMOAD X-ray trial, enrolling 1457 participants with symptomatic knee OA who were randomly assigned to receive 50 or 200 mg of the selective iNOS inhibitor cindunistat/SD-6010 or placebo once daily. Participants were required to have a body mass index (BMI) of 25 to 40 kg/m^2, KLG2 or 3 in the study knee, and at least mild medial JSN with lateral<medial JSN. The current study investigates results in a small subcohort of 66 participants who underwent coronal FLASHwe MR imaging at baseline, of which 62 completed 6M, 47 12M, and 34 24M follow-up. Semi-quantitative readings at baseline and follow-up were performed using the MOAKS system (BICL LLC, Boston, MA). ΔThCtAB from medial and lateral femoro-tibial compartments (MFTC/LFTC), plates, subregions (8 medial, 8 lateral), and ordered values (subregion values within each compartment sorted from greatest thinning to greatest thickening; 8 medial, 8 lateral) were assesses by trained readers, with blinding to time point and treatment group, at a single analysis center (Chondrometrics, Ainring, Germany). Mixed effects models and multivariate analysis of variance (MANOVA) were used to assess differences over all subregions or OVs simultaneously, adjusting for age, sex, BMI, and KLG. ΔThCtAB in MFTC was considered the primary, and medial OVs secondary endpoints; all other (sub)regions were considered exploratory.

RESULTS: At baseline, 92% of the knees had BML, 98% partial cartilage loss, 48% full-thickness cartilage loss, 86% meniscal extrusion, 77% effusion synovitis, and 64% Hoffa synovitis (MOAKS). In the 50/200 mg SD-6010 treatment arms, 60%/61% of the knees, but only 36% in the placebo arm were KLG3. KLG3 knees had more cartilage loss (or less gain) than KLG2 knees, with KLG being the most important covariate explaining variation in ΔThCtAB. At 6M, the mean KLG-adjusted ΔThCtAB in MFTC was significantly different between SD-6010 treatment vs. placebo (p=0.014), and so were medial OVs (p=0.005). ΔThCtAB was similar between 50mg and 200mg SD-6010 arms (MFTC, medial OVs and other endpoints). ΔThCtAB was -5.0±7.8%/+1.8± 11%/ +1.6±6.4% in KLG3 knees in placebo/50mg/200mg arms, and +1.9±7.8%/+6.6±7.0%/+7.1±8.6% in KLG2 knees in placebo/ 50mg/200mg SD-6010 arms. At 12M, only the central lateral femur (p=0.016) but not MFTC (p=0.53) or medial OVs (p=0.43) showed significant differences in ΔThCtAB. At 24M, ΔThCtAB MFTC showed no significant difference between 50/200mg treatment vs. placebo (p=0.58), but medial OVs did (0.013). Differences in medial OVs were somewhat stronger for 200mg vs. placebo (p=0.02) than for 50mg vs. placebo (p=0.05).

CONCLUSION: Results indicate that SD-6010 treated participants appear to have a slower rate of knee cartilage loss or increased cartilage gain in the medial compartment compared with placebo-treated subjects at 6M, and the benefits may extend to 24M follow-up. The reduced level of significance at M12 and M24 could be due to associated reduced sample sizes or changes in individual OA progression or treatment effect over time.

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CONSIDERATIONS WHEN DESIGNING A DMOAD CLINICAL TRIAL USING RADIOGRAPHY

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INTRODUCTION: Despite improvements in our knowledge of the pathological mechanisms underlying OA and improved radiographic protocols, recently completed trials of DMOAD agents have failed to demonstrate efficacy in knee OA. Lack of disease progression in the placebo group as measured by radiographic JSN may hinder the detection of efficacy.

OBJECTIVE: Using placebo data from a recently completed, randomized clinical DMOAD trial, this study sought to inform study design of future radiographic trials.

METHODS: Eligible patients (N=486) were ≥40 years, with body mass index (BMI) ≥25 to ≤40 kg/m^2, and a diagnosis of symptomatic knee osteoarthritis based on Kellgren & Lawrence grade 2 or 3, with pain/stiffness and/or use of medication for knee pain in the past year. Radiographs were acquired using a modified Lyon-schuss (mL/S) protocol at baseline, Week 48 and 96, for assessment of JSN (primary outcome variable). Multifaceted quality control was conducted throughout. Repeat images were requested when the medial tibial plateau (MTP) was not aligned (intermargin distance [IMD] >1.5 mm) or for other quality issues. Data are mean±standard deviation.

RESULTS: Patients (364 female [74.9%]; 83.3% white; aged 61.3±9.1 years) had BMI of 31.6±4.1 kg/m^2 at baseline. In total, 222 (173 females, 49 males) had KLG2, 264 (191 female, 73 males) KLG3. Baseline IMD was 0.536±0.440 mm, and remained consistent throughout. A significant loss in JSW from baseline to week 48 (–0.13±0.36mm) and to week 96 (–0.22±0.46mm) was observed for all randomized patients (P<0.001 for both), and when stratified by KLG (KLG2: -0.08±0.33mm ; P=0.004 and -0.14 ± 0.38; P<0.001; KLG3: -0.16±0.38; and -0.28 ± 0.49; P<0.001 for both, at week 48 and 96, respectively). Standard deviations were small relative to mean changes providing standardized response means of 0.35 and 0.48 at weeks 48 and 96 and when stratified by KLG; KLG2:0.25 and 0.36 and KLG3: 0.42 and 0.56 at week 48 and 96, respectively.

CONCLUSION: Using a tightly controlled, radiographic technique change in JSN is a viable clinical variable for determining OA progression in mild-to-moderate knee OA. The mL/S protocol is a sensitive and feasible protocol for future intervention trials aiming to slow the rate of JSN in the knee by pharmacologic or non-pharmacologic means.

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IDENTIFYING RADIOGRAPHIC PHENOTYPES OF EARLY KNEE OSTEOARTHRITIS USING SEPARATE QUANTITATIVE FEATURES MIGHT IMPROVE PATIENT SELECTION FOR MORE TARGETED TREATMENT

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INTRODUCTION: The expression of osteoarthritis (OA) varies significantly between individuals and over time, implying the existence of different phenotypes.

OBJECTIVE: This study aims at identifying phenotypes of progression of radiographic knee OA and to describe their radiographic and clinical characteristics.

METHODS: In individuals with early knee OA from the Cohort Hip & Cohort Knee (CHECK), baseline, two-year, and five-year follow-up radiographs were evaluated. Separate radiographic OA parameters were quantitatively measured by Knee Images Digital Analysis (KIDA). To identify phenotypes of radiographic knee OA progression, hierarchical clustering was performed using the KIDA measurements of participants with complete data at T0, T2y, and T5y (n=417 of 1002). The phenotypes were compared for development of joint space width (JSW), varus angle, osteophyte area, eminence height, bone density, and for clinical characteristics at T0. Additionally, logistic regression analysis evaluated whether baseline radiographic features predicted to which phenotype an individual belonged.

RESULTS: Overall, the radiographic features showed OA progression during follow-up. Based on the development, five clusters were identified that were interpreted as ‘severe’ (n=17; most progression of all radiographic features) or ‘no’ (n=108) progression, ‘early’ (n=110; progression of all features specifically between T0 and T2y) or ‘late’ (n=69; progression of all features specifically between T2y and T5y) progression, or specific involvement of ‘bone density’ (n=113). Clinical characteristics at T0 were not evidently different between the clusters, and WOMAC scores were only slightly lower in the ‘no’ cluster than in the other clusters. In the evaluation of predictors for the different clusters, the area under the curve (AUC) improved when radiographic features were added to basic demographic and clinical variables. Kellgren & Lawrence grading was not a significant predictor for any of the phenotypes. The predictors for ‘early’, ‘late’, and ‘no’ progression phenotypes generally had an opposite effect than the predictors for the ‘severe’ and ‘bone density’ phenotypes. Larger medial JSW, varus angle, osteophyte area, eminence height, and bone density at T0 were associated with ‘severe’ and ‘bone density’ progression. The AUC of the ‘bone density’ model was 0.91. Smaller eminence height and bone density were associated with ‘early’ and ‘late’ progression (AUC= 0.79, and 0.76 respectively). Larger varus angle and smaller osteophyte area were associated with ‘no’ progression (AUC=0.72).

CONCLUSION: This is the first study to identify specific phenotypes of radiographic knee OA progression in individuals with early OA complaints. Phenotypes represented the level (severe vs. no) and phase of progression (early vs. late), and the involvement of a specific feature (bone density). Baseline radiographic features could predict the phenotypes. The phenotypes might represent relevant subgroups for the evaluation of treatment strategies in clinical trials, and with that drive the discovery of more targeted treatment.

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FULLY AUTOMATIC CARTILAGE MORPHOMETRY FOR KNEE MRI FROM THE OAI

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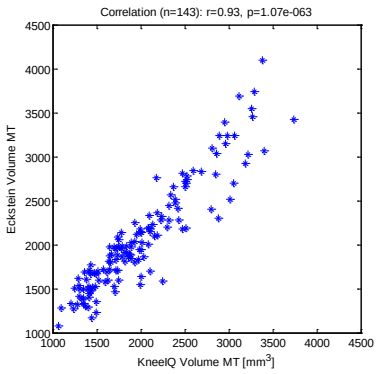
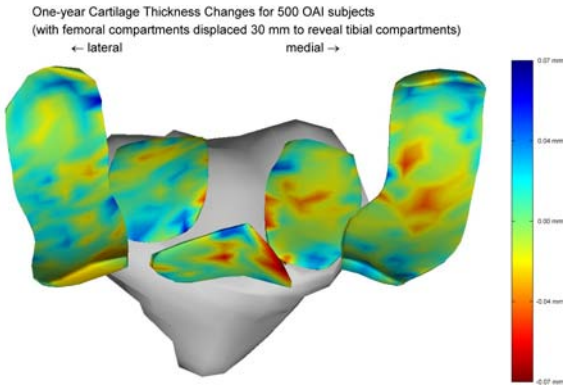
INTRODUCTION: Comprehensive analysis of the Osteoarthritis Initiative (OAI) data has been limited by the overwhelming task of quantifying the 21,000 knee MRI in the multi-visit study with 4,769 participants.

OBJECTIVE: To investigate the feasibility of fully automatic, computer-based segmentation and cartilage quantification on an OAI sub-population including 500 subjects, and further to validate the quantifications against independent measurements from Chondrometrics and VirtualScopics provided by the OAI.

METHODS: The knee MRI were acquired on a Siemens 3T Trio scanner using a sagittal 3D DESS WE sequence (25º flip angle, 16ms RT, 4.7ms ET, 0.36x0.36x0.7 mm voxels, scan time 10 min).
The analysis population of 500 subjects was selected as the first (sorted by patient ID) to have completed the year 0 and year 1 visits. They had age 64±9 years, BMI 28±5, with 36% women. Their Kellgren and Lawrence scores were 38%, 17%, 28%, 15%, and 1% at KL0-4.
The KneeIQ segmentation framework from Biomediq combining statistical texture and shape models was trained and validated on baseline MRI with cartilage segmentations provided by OAI courtesy of iMorphics (50 for training and 33 for validation). For each knee, cartilage volume and thickness maps were quantified for five compartments: patellar and medial/lateral tibial/femoral cartilages.
Further, the quantifications were validated against volume (VC) and thickness (ThCtAB) scores provided by OAI courtesy of Chondrometrics (Eckstein, Wirth) and VirtualScopics (Totterman, Tamez-Peña) for tibial compartments (where all agreed on compartment definitions).

RESULTS: On the iMorphics validation set (n=33), the linear correlations to cartilage volumes for the five compartments were between r=0.78 (for medial femoral) and 0.93 (for lateral tibial). On the overlap with the Eckstein set (n=143), the correlations for medial and lateral tibial volumes were r=0.93 and 0.91, and for medial/lateral tibial thickness 0.86 and 0.88. On the overlap with the VirtualScopics set (n=10), the correlations for volumes were r=0.95 and 0.93, for thickness 0.91 and 0.93. The medial tibial volumes for KneeIQ and Eckstein's measurements are plotted below (left). The one-year cartilage thickness changes for the 500 subjects were moderate with no significant cartilage loss in any compartment (right).





CONCLUSION: We presented results including year 0 and year 1 scans for 500 subjects. The volume and thickness quantification correlated well with gold standard measurements originating from both manual and semi-automated segmentation methods. Thus, we demonstrated the feasibility of complete, automatic quantification of the OAI knee MRI.

SPONSOR: The Danish Research Foundation ("Den Danske Forskningsfond"), Danish Research Councils.
DICLOSURE STATEMENT: The IPR and commercial rights to KneeIQ are with Biomediq.
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ADVANCED MRI-BASED BIOMARKERS OF CARTILAGE LOSS: DATA FROM THE OSTEOARTHRITIS INITIATIVE

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INTRODUCTION: MRI-Based standard measures of average cartilage thickness and volume are typically used to monitor the degree of cartilage loss in OA; however they lack the sensitivity to capture the entire cartilage degradation process. Therefore methods which uses order values, percentile analysis and outlier detection coupled with paired image analysis have the potential to enhance the ability of MRI to monitor cartilage loss.

OBJECTIVE: The purposes of this study are: First, to rank the OA vs. NE discriminant power of global, percentile and outlier analysis, second, to characterize the ability of paired image analysis to separate the degree of annual cartilage changes between an OA disease group and a non-exposed (NE) control group.

METHODS: Selected DESS knee images of the OAI progression subcohort (Group A,B, C and D) and all DESS right knee images from the NE OAI subcohort (Group F) with completed 24 month observations were considered. Progression subcohort knees with paired KL reads, paired qMRI single reader analysis, or paired BLOKS reads and with KL grade scores of 2 or 3 were included. Baseline and 24 month DESS images were segmented using an unsupervised segmentation algorithm and were gender-wise normalized and quantified in the standardized atlas space. Gender-adjusted statistical parametric mapping (SPM) was used to detect areas of cartilage that were statistically different from the average distribution of the NE group. Cross-sectional and longitudinal changes among mean thickness, five percentile (5%) thickness and outlier size were evaluated. Furthermore, paired longitudinal SPM analysis was used to detect areas of cartilage change that were statistically different from the NE behavior. All quantifications were done on the entire Femur (F), the entire Tibia (T), cMF, cLF, MT and LT. The area under the curve (AUC) of the Receiver Operating Characteristic (ROC) analysis was used to evaluate the NE vs. OA discriminant power of the different metrics of cartilage loss.

RESULTS: 181 (81 KL 2; 100 KL 3) progression knees and 111 NE right knees meet the image analysis inclusion criteria. Fig 1 (left) shows the cross-sectional association of the different metrics to separate the NE and the OA group. Fig 1 (right) shows how different longitudinal measures of cartilage loss are able to separate the OA group and the NE group. The average value of the bottom 5% of the femoral cartilage had an AUC ROC of 0.81 (95% CI: 0.76-0.86). The longitudinal paired analysis of cartilage loss had an AUC ROC of 0.91 (95% CI: 0.88 to 0.94).

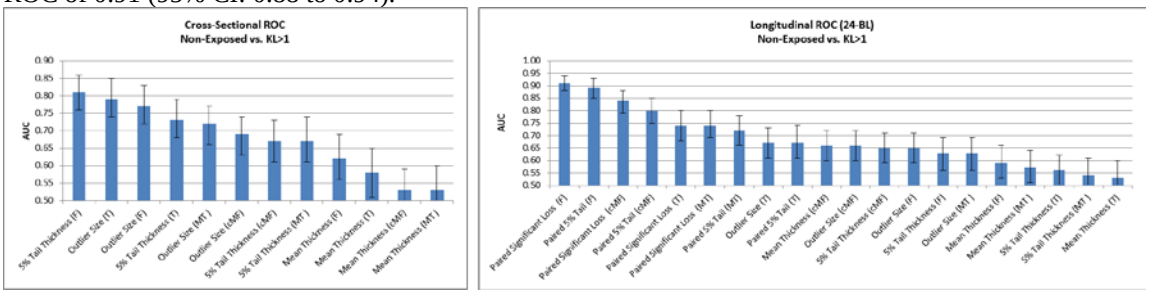

Figure 1: Left cross-sectional ROC AUC of cartilage metrics. Right, ROC AUC of longitudinal analysis of image-paired and image-unpaired metrics.

CONCLUSION: Advanced measurements from the entire cartilage plates are better powered to separate an OA group from NE group than regional analysis. Further, paired image-analyses of the entire cartilage plates is superior to un-paired image analysis for the analysis of longitudinal changes.

SPONSORS: OAI-NIH (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262)
DICLOSURE STATEMENT:
ACKNOWLEDGEMENTS:
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RESPONSIVENESS OF A SEMI-AUTOMATED NOVEL METHOD OF MEASURING CARTILAGE LOSS IN KNEE OSTEOARTHRITIS OVER TWO YEARS USING 3T DESS 3D MRI

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INTRODUCTION: Methods to accurately, quickly, and inexpensively detect cartilage loss are critical to facilitate the use of imaging biomarkers in assessment of OA severity and progression, and are important in large OA trials and observational research. For example, the OAI has over 38,000 individual 3D MRI scans in the first five visits. It is critical that fast and responsive methods are available to provide a complete assessment these data. We have developed a method to measure cartilage loss in focused sub-regions, determined with respect to a 3D cylindrical coordinate system (a 3D analogue to the previously reported Cartesian coordinate system used to improve measure radiographic location-specific joint space width in the knee).

OBJECTIVE: The purpose of this study was to validate the responsiveness and efficiency of a novel semi-automated method to detect knee cartilage loss over 2 years in subjects with established knee OA.

METHODS: Twenty-four subjects from the OAI Progression Cohort (Data Set 0.1.1 and Image Releases 0.B.1 and 1.B.1) were randomly selected. Inclusion criteria were a baseline KL grade of 3. An independent reader (CR) used the software method to segment the medial compartment of the femur from the baseline and 24-month visits, blinded to order of visit. Double echo steady state (DESS) 3D sagittal images were obtained on a 3T Siemens Trio MR system (0.365 mm x 0.365 mm, 0.7 mm slice thickness, TR 16.5 ms, TE 4.7 ms). The primary outcome was the change in cartilage volume from baseline to follow-up, measured at a fixed point with respect to the coordinate system. Change was measured for 7 regions of varying surface area centered on the fixed point selected by an independent reader (experienced radiologist) for cartilage degradation. The performance was quantified by calculating the standardized response mean (SRM) and the percentage of subjects for which there was a net loss of cartilage.

Surface area of region (mm^2)	Standard Response Mean (SRM)	% with net cartilage loss
450	-0.63	0.79 (19/24)
350	-0.62	0.75 (20/24)
250	-0.67	0.79 (19/24)
170	-0.59	0.71 (17/24)
110	-0.52	0.83 (20/24)
60	-0.51	0.79 (19/24)
20	-0.44	0.71(17/24)

Table 1 Cartilage loss in 6 regions and for the total medial femoral compartment. The SRM, and the percentage of subjects for which cartilage loss was measured.

RESULTS: Results are presented in Table 1. All regions showed a net cartilage loss from baseline to 24 months, averaged over all subjects. Approximately 80% of individual subjects showed a net cartilage loss. The average reading time was 10.5 minutes per knee (SD 3.4) (25-30 slices).

CONCLUSION: The results confirm that measurement of cartilage loss in a local region is responsive (SRM = -0.67) and that a coordinate system can potentially be used to objectively explore and establish a consistent location at the knee that is most responsive to change in cartilage volume. This technique has the potential to provide an objective quantitative measure of cartilage loss rapidly and accurately - making it feasible, for example, to assess over 1,000 knees in less than two months. This could substantially reduce study costs and increase study power for large trials and datasets such as the OAI.

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DICLOSURE STATEMENT: None
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IN VIVO DTI OF ARTICULAR CARTILAGE AS A BIOMARKER FOR OA

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INTRODUCTION: Diffusion tensor imaging (DTI) of articular cartilage has been proposed as an OA biomarker for both the proteoglycan content and the collagen architecture. The key idea behind the use of DTI is that the different components of the cartilage matrix leave a different imprint in the motion of water molecules. The random orientation of the highly compressed proteoglycan molecules induces an isotropic restriction on water diffusivity which reflects in the mean diffusivity (MD). The highly organized collagen architecture of cartilage leads to anisotropic water diffusion. Thus, any measurement of the diffusion anisotropy (e.g. the fractional anisotropy, FA) is a measurement of the collagen architecture.

PURPOSE To assess the potential value of in vivo diffusion tensor imaging (DTI) of articular cartilage for the early diagnosis of OA as compared with the widely used T2 relaxation time.

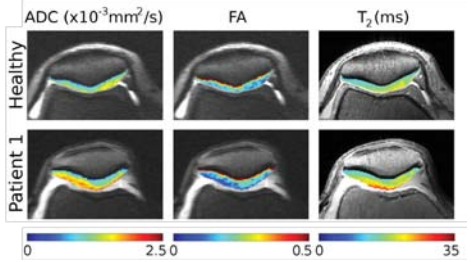

Figure 1: Example of MD, FA and T2 maps of a healthy volunteer (31 y, male) and a OA subject (60 y, female).

METHODS: The patellar cartilage of 16 healthy volunteers (30.7±2.3 y, no episodes of knee pain, no history of trauma) and 10 OA-diagnosed patients (62.6±8.8 y) from the NYU-HJD cohort with subtle signal abnormalities and absence of cartilage erosion in clinical MRI were imaged on a whole body 7-T scanner with a birdcage transmit, 28-channel receive knee coil. 10 of the patients were imaged two times to assess test-retest reproducibility as the root-mean-square of the coefficient of variation. The MRI protocol included a high-resolution (0.5 mm isotropic) $T2^*$-weighted FLASH sequence, a Line Scan Diffusion Imaging sequence for DTI measurement (6 diffusion directions, b-values=5,450 s/mm^2, resolution=0.6×0.6×2 mm^2, 5 slices) and a multi-slice multi-echo sequence for T2 calculation (TE=16 ms, echo train length=8, resolution=0.6×0.6×2 mm^2, 5 slices). Cartilage was segmented and maps (T2, MD and FA) were calculated. The segmented cartilage was divided into 2 layers parallel to the bone-cartilage interface and four consecutive sectors from medial to lateral, which resulted in a total of 8 regions. Differences between the MRI parameters in the healthy and OA collectives were assessed with the non-parametric Wilcoxon test globally (averaged over all the slices), by layers, by sectors. ROC-curve analysis was used to assess the ability of each MRI parameter to discriminate healthy from OA patients.

RESULTS: In healthy volunteers ADC decreased from the articular surface (1.2±0.3) 10^{-3} mm²/s to the bone-cartilage interface (0.6±0.3) 10^{-3} mm²/s. FA increased form the surface (0.2±0.1) to the deep radial zone of the cartilage (0.5±0.3). Test-retest reproducibility was better than 10% for mean ADC (8.1%), FA (9.7%) and T2 (5.9%). Globally, ADC and FA differed significantly ($P<0.01$), between the OA and the healthy collective (Healthy: ADC (1.00±0.10)×10^{-3} mm^2/s, FA (0.30±0.04); OA: ADC (1.29±0.16)×10^{-3} mm^2/s, FA (0.22±0.05)), but T2 (Healthy: (22.9±4.2) ms; OA: (21.7±2.9) ms). An optimal threshold of 1.2×10^{-3} mm^2/s for ADC allowed to differentiate both populations with a specificity of 0.81 (13/16), a sensitivity of 0.90 (9/10). The same analysis for FA yielded an optimal cutoff of 0.26 (specificity = 0.88 (14/16), sensitivity = 0.80 (8/10)). T2 showed a low ability to differentiate (specificity = 0.68 (11/16), sensitivity = 0.60 (6/10)) From all 40 regions (5 slices×8 regions), 20 (50%) had significantly increased ADC, 14 (35%) had significantly reduced FA, but only one (3%) showed significantly increased T2.

CONCLUSION: In vivo DTI of articular cartilage provides new biomarkers for the early diagnosis of OA. In our study DTI discriminated both populations more accurately than the T2 relaxation time.

SPONSOR: None.
DICLOSURE STATEMENT: None.
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SIGNAL-TO-NOISE IMPACTS THE ACCURACY AND PRECISION OF KNEE ARTICULAR CARTILAGE T2 RELAXATION TIME MEASUREMENTS

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INTRODUCTION: The SNR improvement at 3T was thought to be particularly advantageous for articular cartilage morphometry and T2 measurements for the Osteoarthritis Initiative (OAI). For this reason and because T2 is often used for compositional assessment of cartilage, the role of SNR on the accuracy and precision (reproducibility) of cartilage spin-spin relaxation times was evaluated by comparing measurements made using two knee coils with different SNR characteristics.

OBJECTIVE: Determine the accuracy and precision of cartilage T2 measurements under conditions of different SNR.

METHODS: 12 knees were examined in 10 individuals; six knees met OAI progression and six knees met incident cohort definitions. Images were acquired on 3T MR systems (Siemens Magnetom Trio) using both a quadrature-transmit (QTR; USA Instruments Inc) and a quadrature-transmit/eight-channel phased-array receive (QT8PAR; InVivo Corp) knee coil. Imaging was performed as in the OAI including two morphologic 3D series as well as a sagittal multi-slice, multi-echo spin echo (MSME-SE) acquisition for T2 measurement. Each subject underwent four MR exams. On one day, a test-retest examination was performed using one of the two coils. Between the two MR exams the participant was removed from the magnet. Within 1 month of the first MR exam, the same acquisitions were repeated using the other coil. T2 values were computed pixel-by-pixel using custom software written using IDL (Exelis Visual Information Solutions). Four regions (MT, LT, cMF, cLF) in each knee were defined by manual cartilage segmentation. To understand the influence of SNR on T2 values, signal intensities (SI) in cartilage and bone marrow and the noise levels for both the medial and lateral sides of the knee were measured. Statistical significance was tested using a paired Student's t-test. Re-measurement error (precision) was quantified using the root-mean-square coefficient-of-variation (RMS CV%).

RESULTS: The SNR was significantly higher ($p<0.001$) using QT8PAR for ROIs measured on the last echo images (TE=70ms). T2 values for cMF (45.9ms/50.7ms) and MT (41.6ms/48.2ms) as well as muscle (37.9ms/40.7ms) were significantly longer with QT8PAR ($p<0.0004$). No significant difference in T2 values was found for cLF and LT cartilage ($p=0.06$ and $p=1.0$) or MT epiphyseal marrow ($p=0.77$). The T2 precision was better ($p<0.001$) for the cLF, cMF, and infrapatellar fat when using the QT8PAR coil.

CONCLUSION: Knee articular cartilage T2 values varied spatially, with cLF having the longest value (52ms) and LT having the shortest (40.6ms). SNR can vary spatially depending upon coil. Under conditions of higher SNR, significantly longer T2 values were measured; this was particularly evident for deep cartilage layers as well as cMF. This effect can be larger than the impact of changing magnetic field strength.

SPONSOR: The funding source, NIAMS, had input into the study design and data collection methods, but otherwise did not participate in the study. All data analysis and interpretation, manuscript writing and decision to submit for publication were the sole responsibility of the authors.
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ACKNOWLEDGMENT: The OAI and this pilot study are conducted and supported by NIAMS in collaboration with the OAI Investigators and Consultants. The research reported in this abstract was supported in part by contracts N01-AR-2-2261, N01-AR-2-2262 and N01-AR-2-2258. We are grateful to the Ohio State University and Memorial Hospital of Rhode Island OAI study teams for recruitment of the study subjects and acquisition of the MR exams.
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VALIDATION OF AN OBJECTIVE, ANALYST-INDEPENDENT, NON-INVASIVE METHOD FOR ASSESSING EFFECTIVENESS OF CARTILAGE REPAIR THERAPIES IN MULTICENTER RCTS

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INTRODUCTION: Assessment of structural repair resulting from cartilage repair therapies as an RCT endpoint is confounded by qualitative and categorical imaging scoring methods, or by the risks and challenges associated with obtaining post-treatment and longitudinal biopsies.

OBJECTIVE: To present a comprehensive approach to novel and validated imaging-related support of randomized clinical trials (RCTs) for cartilage repair therapies.

METHODS: Imaging data (n=80) was obtained 1 and 12 months post-treatment during an international, multicenter RCT of cartilage repair of defects in the knee (Piramal Healthcare (Canada)). Sources of potential variance were identified and controlled within the trial with use of standardized protocols for collecting GRE, SPGR and Dual Echo Spin Echo MRI images from 13 MRI sites that were monitored to ensure protocol conformity and geometric accuracy of image data. T2 phantom data was acquired in the field of view of all study subject scans. Segmentation methods were validated and published by statistical comparison of morphological measurements to published data and by comparing longitudinal change in measurement to semi-quantitative expert scoring [1]. Analysis workflow was validated by generating measurements from a subset of trial data and comparing results to those obtained in a previous sub-study of the same data. MRI data automatically segmented for bone and cartilage were edited by an expert analyst to identify defect and repair cartilage boundaries. Quantitative measurements of defect volume, defect %Fill and T2 were obtained from the final segmentations, yielding endpoints of both repair cartilage quantity and quality. Results of analysis for treated defect %Fill, defect volume and T2 were validated by having two independent radiologists with expertise evaluating cartilage repair perform all analysis procedures on a subset of data from 30 patients, including 10 blinded and repeated patients' data. The repeated data provided the basis for intra- and inter-reader precision estimates using Pearson's correlations. Availability of 38 osteochondral biopsies obtained from treated defects at 13 months permitted an evaluation of potential associations between T2 with matched histological and MRI structural data using linear and non-linear statistical models.

RESULTS: Segmentation methods were cross-validated and published[1]. Inter-and Intra-reader analyses correlated highly with Pearson's coefficients ranging from 0.85 (%Fill) to 0.99 (Defect volume). Both radiologists agreed on estimation of defect %Fill with near zero systematic differences (rho=0.83). Analyses from both radiologists for estimated T2 values agreed, yielding no statistical differences (rho=0.99). ANCOVA analysis found both PLM and %Fill to be significant co-factors in explaining the T2 response (p=0.013 and p=0.003 respectively), revealing a multiple correlation coefficient of R=0.62, which importantly was independent of treatment.

CONCLUSION: Structural cartilage repair RCT imaging endpoints necessitate control of variability, reliable quantification and precision. Our MRI methodology has been validated here to provide objective evidence of cartilage repair endpoints of tissue quality and quantity. Scientific validation of T2 analysis was achieved by correlation to matched biopsy tissue structure.

SPONSOR: Piramal Healthcare (Canada), LTD
DISCLOSURE STATEMENT: Authors are affiliated with respective commercial entities as indicated.
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[1] Tamez-Pena J. et al. **"**Atlas based method for the automated segmentation and quantification of knee features: Data from the osteoarthritis initiative" IEEE, ISBI, pp 1484 – 1487, 2011

LONGITUDINAL CHANGES IN CARTILAGE REPAIR TISSUE QUANTITY AND QUALITY BY QUANTITATIVE MRI

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INTRODUCTION: It is a longstanding orthopedic belief recently supported by clinical literature that improving repair cartilage structure will lead to longer durability and sustained clinical benefit. However, the maturation process in cartilage repair is to a large extent unknown and thus longitudinal studies are needed. Two critical structural characteristics of new repair cartilage are its quantity and quality. Quantitative MRI can assess the volume of new tissue within a cartilage defect from which the degree of filling can be calculated. T2 relaxation time assesses collagen macromolecular concentration, orientation and hydration, and can indicate overall collagen network architecture, a key determinant of cartilage mechanical properties and durability. T2 MRI can also identify zonal depth-dependent stratification in repair cartilage.

OBJECTIVE: To investigate longitudinal changes in new repair cartilage quantity (%Fill) and quality (T2) following treatment with 2 different cartilage repair procedures using quantitative MRI.

METHODS: An international multicenter randomized clinical trial (RCT) for cartilage repair compared treatment with microfracture to BST-CarGel®, a chitosan-based medical device. Eighty patients (BST-CarGel n=41, microfracture n=39) with grade 3/4 focal defects on the femoral condyles were enrolled into the RCT, and data from 29/80 (BST-CarGel n=15, microfracture n=14) was available at 3 years post-treatment from a long-term extension study. Standardized MRI scans from this cohort at 1 month (representing defect baseline), 1 and 3 years post-treatment, included 3D fat-suppressed SPGR and 3D-GRE for morphological analysis, and fat-suppressed Dual Echo Spin Echo for T2 mapping. Following 3D reconstruction and morphological segmentation, defect %Fill was calculated from the ratio of debrided defect volume at 1 month to repair tissue volume at 1 and 3 years using co-registration. Quantitative biomarkers were extracted from ipsilateral native cartilage, baseline defects and new repair tissue which reflected quantity and quality including % Fill, mean T2 (calculated from the entire 3D tissue volume), and T2 strata comprising the upper and lower 50% of the repair tissue volume. Means adjusted for baseline defect volume were compared with ANCOVA.

RESULTS Defect filling (%Fill) increased in both groups from 1 to 3 years post-treatment, respectively from 92.1% to 96.7% for BST-CarGel and 85.2% to 88.0% for microfracture. Filling was significantly greater for BST-CarGel compared to microfracture at both 1 and 3 years (p=0.0105 and 0.033 respectively). Mean T2 values from repair tissues shortened from 1 to 3 years post-treatment in both groups, from 67.6ms to 64.6ms and 85.6ms to 82.0ms for BST-CarGel and microfracture respectively, but T2 values for BST-CarGel were closer to native cartilage compared to microfracture (p=0.054 and 0.016). T2 stratification showed that, compared to microfracture tissue, BST-CarGel tissue exhibited zonal stratification that further resembled native cartilage from 1 to 3 years, as opposed to microfracture which became less stratified.

CONCLUSIONS: Longitudinal analysis of cartilage repair in a patient cohort from an RCT has demonstrated for the first time using quantitative MRI that the growth and maturation process in repair cartilage continues even after 1 year post-treatment. While improvements in the collagen organization of repair cartilage over time may be expected, continued defect filling over time is currently undescribed. Furthermore, compared to microfracture, BST-CarGel treatment resulted in statistically more repair cartilage, characterized by superior collagen content and stratification.

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DICLOSURE STATEMENT: Shive is a consultant to Sponsor.
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CORRESPONDENCE ADDRESS: Matthew Shive, PhD, Shive@videotron.ca, 514-826-6716

EFFECTS OF TRAINING INTERVENTION ON QUADRICEPS HEADS IN PERI-MENOPAUSAL WOMEN

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INTRODUCTION*:* Quadriceps strength was found to protect against the onset of symptomatic knee osteoarthritis, and the vastus medialis (VM) muscle has been proposed to be of particular importance in biomechanically stabilizing the knee.

OBJECTIVE: To determine whether training effects on anatomical muscle cross sectional areas (ACSAs) differ between the four quadriceps heads, whether training reduces the extracellular fat, and whether such a reduction can be assessed based on muscle signal intensity (SI) in T1-weighted SE MR images.

METHODS*:* 35 untrained peri-menopausal women (age 45-55y) were randomly assigned to a supervised endurance training (cycling, n=19) and strength training (lower body, n=16), 3 times per week for 60 min. over 12 weeks. Axial MR images (1.5T) of the entire thigh were acquired before and after training intervention, using a T1-weighted turbo spin echo (TSE) sequence and 10mm slice thickness. ACSAs and SI were determined for the VM, vastus inter-medius (VIM), vastus lateralis (VL), and rectus femoris (RF) in the distal half of all slices between the quadriceps tendon and the proximal end of the femoral neck. Additionally we studied the SI of the VL at baseline and follow-up, and their correlation with extracellular fat, determined by light microscopy.

RESULTS*:* Across all study participants, the increase in ACSAs by training intervention was +3.8% in the VM, +0.9% in the VL, +1.7% in the VIM, and +1.2% in the RF, with the VM and VIM showing a statistically significant increase over 12 weeks ($p<0.05$). The differences in response (% increase by exercise intervention) between the quadriceps heads did not reach statistical significance ($p=0.27$; ANOVA repeated measures). There was no significant change in the SI (mean or standard deviation = SD) or the percentage of extracellular fat in any of the quadriceps heads within training groups. A negative correlation was observed between the SI of the VL and the percentage of extracellular fat at baseline ($r=-0.37$) and at follow-up ($r=-0.40$), as well as for change in VL SI vs change in extracellular fat between baseline and follow-up ($r=-0.42$). Training effects on quadriceps heads for strength vs. endurance training are shown in Table 1.

Table1: Mean ± standard deviation (SD; *%*) and p-values of the change in anatomical muscle cross sectional areas (ACSAs) and muscle signal (SI) over a 12 week training period (changes significant at $p<0.01$ are marked with *); Vast.Med. = vastus medialis; Vast.Lat. = vastus lateralis; Vast.Int.med = vastus intermedius; Rect.Fem.= rectus femoris

		Both		**Endurance**		**Strength**	
		Mean±SD	**p**	**Mean±SD**	**p**	**Mean±SD**	**p**
ACSAs in cm²	Vast.Med.	3.8±4.0	0.000004*	4.9±4.6	0.0002*	2.5±2.7	0.003*
	Vast.Lat.	0.9±8.8	0.75	1.9±9.8	0.49	-0.2±7.6	0.64
	Vast.Int.med.	1.7±3.8	0.017*	1.8±3.6	0.05	1.6±4.2	0.18
	Rect.Fem.	1.2±11.1	0.69	0.9±11.5	0.95	1.7±11.0	0.61
SI (*Mean*)	Vast.Med.	1.0±7.7	0.64	3.1±7,4	0.11	-1.4±7.6	0.32
	Vast.Lat.	1.8±8.1	0.40	4.0±8.2	0.06	-0.8±7.5	0.47
	Vast.Int.med.	1.3±9.9	0.72	4.3±9.6	0.08	-2.2±9.4	0.27
	Rect.Fem.	-1.0±8.0	0.32	0.6±7.8	0.79	-2.9±8.0	0.10
SI (*SD*)	Vast.Med.	1.0±14.8	0.94	4.8±16.9	0.30	-3.5±10.7	0.09
	Vast.Lat.	3.3±16.3	0.42	6.2±17.0	0.16	-0.1±15.2	0.77
	Vast.Int.med.	2.6±15.9	0.43	5.2±19.5	0.33	-0.4±10.0	0.85
	Rect.Fem.	0.4±12.1	0.85	2.4±12.8	0.59	-1.8±11.2	0.41
Extracellular fat (*%*)	Vast.Lat.	0.3±1.3	0.73	0.2±0.8	0.47	0.5±1.6	0.80

CONCLUSIONS*:* To our knowledge, this is the first study to explore differential training effects on the four quadriceps heads. The data indicate that the exercise-induced increase in ACSAs may be somewhat stronger for the vastus medialis (VM) than for the vastus lateralis (VL). No significant alterations in MRI SI and extracellular fat were found during the exercise intervention and no positive correlation between SI and extracellular fat.

SPONSOR: none
DICLOSURE STATEMENT: See affiliations

COMPARISON OF MUSCLE AREA AND STRENGTH BETWEEN OA KNEES WITH AND WITHOUT STRUCTURAL PROGRESSION - DATA FROM THE OA INITIATIVE

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INTRODUCTION: Quadriceps strength was reported to protect against the onset of symptomatic knee OA, but whether it protects against structural progression once OA is established radiographically is unclear.

OBJECTIVE: To determine whether baseline (BL) differences or two-year changes in anatomical muscle cross sectional areas (ACSAs) of the quadriceps (heads), hamstrings, and adductors, and/or muscle strength of the extensor and flexors differ between OA knees with structural progression (both cartilage loss in MRI and JSW loss in X-rays) compared with OA knees without structural progression (in MRI or X-rays).

METHODS: 561 knees from the OAI with BL and one-year cartilage thickness (ThCtAB) (MRI) and radiographic JSW measurements, and central KL readings were selected. Of these, 46 showed structural progression in medial ThCtAB and JSW (smallest detectable change method). Controls were found for 20 of the 23 KLG 2/3 knees, for which BL and year 2 axial T1-weighted SE thigh MRIs and muscle strength measurements (Good Strength Chair) were available (matching criteria: same sex and KLG, body height ±3cm, BMI±5kg/m², WOMAC pain±5 units). ACSAs (Table 1) and signal intensities of the thigh muscles were determined independently at BL and at year 2 at 33% femoral length (from distal; estimate based on body height) and those of the four quadriceps heads at 30% femoral length and compared with paired t-test.

RESULTS: Cases with MRI and X-ray progression (age 63.1±7.8 y) and controls without progression (age 65.8±10.0 y) included 12 women and 8 men, respectively. ACSAs of the total quadriceps, the quadriceps heads, the flexors, and the adductors and extensor and flexor strength at BL did not differ significantly between cases and controls ($p<0.05$; Table 1). None of the muscles showed differences in mean or SD MR signal intensity (data not shown). Changes in ACSAs and signal over 2 years also did not significantly differ between progressors and non-progressors (Table 1). When stratifying for BL WOMAC pain, findings were similar for cases with pain scores of 0-1 (n=7) and those with scores of 5-8 (n=8; data not shown).

Table 1: Thigh Muscle ACSA and Strength in Knees with and without Structural Progression

ACSA in cm²	BL mean ±SD				Mean change (BL→year 2) ±SD			
Strength in N	Progr.	Non-progr.	%-diff	p	Progr.	Non-progr.	%-diff	p
Quadricps	46.1±14	46.2±12	4.0±24	0.96	-3.9±9.7%	-2.7±7.2%	5.8±30	0.68
Vastus med.	17.9±4.8	17.1±4.0	-0.8±25	0.46	-4.7±11%	-3.1±12%	3.0±18	0.69
Vastus lat.	11.3±5.0	12.2±4.7	19±43	0.39	-3.5±16%	-0.4±11%	-1.4±2.9	0.45
Vastus intermed.	12.7±3.8	12.6±3.1	4.5±29	0.95	-1.1±9.2%	-3.0±11%	-0.4±1.5	0.5
Rectus Femoris	1.4±0.8	1.8±1.3	61±132	0.21	6.4±45%	-1.0±38%	-1.7±4.3	0.64
Hamstrings	33.2±9.5	30.1±7.8	-6.7±20	0.07	-0.4±6.7%	-3.0±6.8%	-1.0±6.2	0.24
Adductors	10.8±6.6	9.6±4.9	8.5±79	0.39	-0.2±22%	0.1±31%	0.4±4.8	0.96
Extensor strength	344±94	349±129	2.5±30	0.83	-2.8±22%	-9.9±27%	-1.6±2.0	0.46
Flexor strength	138±43	140±65	7.2±48	0.87	-8.0±37%	-12±32%	2.4±11.4	0.8

CONCLUSION: Progressor and non-progressor knees were carefully selected from a large sample, based on two independent methods for assessing structural OA progression (MRI and X-rays). Further, knees were carefully matched for variables known to be associated with progression or AMCSAs. The results of this exploratory study do not provide support that BL differences or longitudinal changes in thigh muscle ACSAs or strength predict (or are associated) with structural progression in knees with radiographic OA.

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HOW TO QUANTIFY THE SENSITIVITY OF MRI T1ρ and T2 RELAXATION MEASUREMENT IN CARTILAGE DEGRADATION?

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INTRODUCTION: How can one quantify the sensitivity of MRI T1ρ or T2 relaxation measurements in cartilage degradation? Is the percentage change in the values an accurate indicator? For example, when T2 increases from 30ms to 60ms, it would be a significant 100% increase. However, can one have the same confidence when T2 increases from 3ms to 6ms, still the same 100% increase? Or is the absolute change in the relaxation values a better indicator? A number of practical issues can reduce the reliability of either parameter when it is used alone.

OBJECTIVE: A more reliable indicator for the sensitivity in MRI relaxation measurement should consider both the percentage changes and the absolute changes in the measurement.

METHODS: Six humeral tissue blocks were harvested and paired from three mature and healthy dogs. All specimens were first imaged by the same imaging protocol as their own controls. After the initial MRI, one specimen from each pair was immersed in 1mM Gd-DTPA^{2-} (Magnevist) solution in saline with 1% protease inhibitor before a repeating MRI. The other specimen in the pair was first soaked in 0.1mg/ml trypsin solution to deplete proteoglycans (PG) and then soaked in saline to remove excess trypsin before the repeating MRI. After the repeating MRI, the PG-depleted specimen was immersed in Gd-DTPA^{2-} and subsequently imaged for the third time. Microscopic MRI (μMRI) experiments were carried out on a Bruker AVANCE II 7T micro-imager, with an acquisition matrix of 256×128 (13×26 μm pixel resolution) and a slice thickness of 1 mm. Other acquisition parameters followed the published protocols.

RESULTS: 2D T1ρ and T2 images were calculated for all specimens. The depth-dependent profiles were analyzed at the depth-resolution of 13μm. Based on the published criteria, the relaxation profiles were divided into four structural zones (superficial, transitional, up radial, low radial). The zone-averaged relaxation values were tabled and analyzed statistically. A quantity termed *Sensitivity* was defined as,

$$\text{Sensitivity} = \text{Percentage-Ratio} \times \text{Absolute-Change}$$

where the *Percentage-Ratio* is $(T_{after} - T_{before})/T_{before}$ in percentages, and the *Absolute-Change* is $(T_{after} - T_{before})$ in ms in this project. This quantity has the form of an equilateral hyperbola and can be plotted as a set of 2D contours, where each hyperbola equals a constant *Sensitivity* and the diagonal line points to an increasing *Sensitivity*. It can be shown that this combined quantity *Sensitivity* can differentiate the measurement sensitivities in both T1ρ and T2 measurements: Any data point (i.e., experimental condition) that is not near one of the axes or the origin is sensitive in the relaxation measurement. Four sets of experimental conditions in this micro-imaging project were analyzed: (a) degraded – native, (b) degraded with Gd – degraded, (c) native with Gd – native, and (d) degraded with Gd – native with Gd. Several distinct features can be identified. First, T2 has sufficient sensitivity in all zones at 55° but only in TZ at 0° (a) for the first and second sets of experimental comparisons. Second, T1ρ at high spin-lock powers has sufficient sensitivity in all zones at both 0° and 55° for the first and second sets of experimental comparisons (b). Neither T2 nor T1ρ has sufficient sensitivity for the later two sets of comparisons (c, d).

CONCLUSION: It was found that a combined quantity, *Sensitivity*, can better determine the T2 and T1ρ sensitivities in native and trypsin-degraded articular cartilage. T1ρ values (especially at high spin-lock power) were sensitive to PG loss regardless of the specimen orientation in the magnet. The sensitivity of T2 measurements to PG loss depended on the fibril orientation (more sensitive at the magic angle than at 0º) and the depth of cartilage (at 0°, more sensitive at TZ than SZ and RZ; at 55°, nearly uniform sensitivity).

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PLASMA LEPTIN AND RESISTIN MAY PLAY A ROLE IN EARLY-STAGE KNEE OSTEOARTHRITIS: DATA FROM CHECK, A COHORT OF EARLY OSTEOARTHRITIS.

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INTRODUCTION: There is ambiguous data on the involvement of adipokines in osteoarthritis (OA).

OBJECTIVE: To investigate the potential relevance of adipokines in development and/or progression of (very) early knee OA.

METHODS: Baseline plasma leptin, adiponectin, and resistin levels were assessed by ELISA in samples from CHECK (Cohort Hip and Cohort Knee), a prospective cohort of 1002 individuals with symptoms of (very) early knee and/or hip OA.
Baseline biomarkers of cartilage and synovial metabolism were assessed by ELISA or RIA (Cartilage: uCTX-II, sPIIANP, sCS846. Synovial tissue: sHA, sPIIINP. Cartilage/synovial tissue: sCOMP).
Knee radiographs were obtained at baseline and after 2 and 5 years. OA burden was expressed as the summed Kellgren & Lawrence (K&L) grade for both knees at baseline. OA progression was expressed as the area under the curve (AUC) of summed K&L grades during 5-year follow-up.
Associations with presence of knee OA and occurrence of knee OA incidence and progression were investigated by binary logistic regression (OA burden: summed K&L grade 0 vs $\geq$1, incidence and progression: AUC 0 vs >0 in subjects without and with knee OA at baseline, respectively). Associations with the extent of knee OA burden, incidence, and progression were investigated by linear regression.

RESULTS: Data were complete for approximately 800 participants at baseline and 725 participants at all time points.
Leptin and resistin were negatively associated with adiponectin and positively associated with each other. Likewise, both leptin and resistin were positively associated with hsCRP, while adiponectin was negatively associated with hsCRP.
Leptin showed statistically significant but weak positive associations with uCTX-II, sCOMP, sPIIANP, sHA, and sPIIINP (max stand beta=0.279, P<0.001). Leptin showed statistically significant but weak positive associations with presence but not extent of knee OA (OR/unit=1.016, 95% CI=1.006-1.025) and with occurrence but not extent of knee OA progression (OR/unit=1.020, 95% CI=1.006-1.034), that disappeared after adjustment for BMI.
Adiponectin was statistically significantly positively associated with sCOMP and uCTX-II (max stand beta=0.150, P<0.001), but not associated with radiographic knee OA burden, incidence, or progression.
Resistin showed a statistically significant association with sPIIINP only (stand beta 0.127, P<0.001), but was associated with presence but not extent of radiographic knee OA burden (OR/unit=1.222, 95% CI=1.084-1.379) and occurrence but not extent of incident knee OA (OR/unit=1.261, P=0.015). As opposed to leptin, these associations did not change after adjustment for BMI.

CONCLUSION: Leptin and resistin showed the most associations with biomarkers and radiographic knee OA. Leptin may function as a humoral mediator between knee OA and BMI, while resistin especially showed an effect on knee OA independent of BMI. The low grade of all associations may be partly due to the limitations of biomarkers and radiographic disease measures in early-stage OA. Nevertheless, these data indicate that systemic adipokines could be involved in early-stage knee OA development and progression.

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CORRELATIONS OF CTX-II WITH BIOCHEMICAL MARKERS OF BONE TURNOVER RAISE QUESTIONS ON ITS TISSUE ORIGIN: DATA FROM CHECK, A COHORT OF EARLY OSTEOARTHRITIS.

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INTRODUCTION: Biochemical markers (biomarkers) are proposed to reflect certain metabolic pathways in health and disease. However, actual molecular validity of biomarkers is often not definite.

OBJECTIVE: uCTX-II has been put forward as a marker of collagen type II degradation being part of cartilage degradation in osteoarthritis and is used as (surrogate) end point in therapeutic trials. Here we present data that argue against this assumption and warrant more cautious interpretation of uCTX-II levels.

METHODS: uCTX-II, and the bone biomarkers uCTX-I, uNTX-I, sPINP and sOC as well as the cartilage markers sCOMP, sCS846, and sPIIANP were assessed by ELISA in baseline samples of CHECK (Cohort Hip & Cohort Knee), a cohort of 1002 individuals with early complaints of pain and/or stiffness in knee and/or hip. Correlations between biomarkers and between biomarkers and demographics were investigated through linear regression.

RESULTS: uCTX-II was more strongly correlated with bone markers than with the cartilage markers, while the cartilage markers did not show such strong correlations with the bone markers. Moreover, both uCTX-II and bone markers but not the other cartilage markers showed an abrupt menopausal shift in woman at the age of 50-55 years, also when adjusted for age and BMI.

CONCLUSION: The increased bone marker levels in postmenopausal women are in accordance with the well-known increase in bone turnover after menopause. The many similarities between uCTX-II and bone markers could be attributable to a link between cartilage and bone metabolism through metabolic and biomechanical mechanisms. However, other cartilage markers were hardly correlated with uCTX-II and did not show such evident correlations with bone markers. These data suggest that uCTX-II has unique relations with bone markers as compared to other cartilage markers and reflects bone rather than cartilage metabolism. Accordingly, other authors have suggested osteoclastic resorption of calcified cartilage as the major origin of uCTX-II. More thorough molecular validation of uCTX-II is required to better define its origin. Until then, uCTX-II levels should be interpreted cautiously.

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CLUSTERS WITHIN A WIDE SPECTRUM OF BIOCHEMICAL MARKERS FOR OSTEOARTHRITIS: DATA FROM CHECK, A COHORT OF EARLY OSTEOARTHRITIS.

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INTRODUCTION: Current knowledge of biochemical markers (biomarkers) for osteoarthritis (OA) is mainly based on data from small cohorts and/or only one or a few simultaneously assessed biomarkers. The potential value of simultaneous assessment of multiple biomarkers is increasingly recognized.

OBJECTIVE: To assess a wide spectrum of biomarkers in a large cohort of individuals with (very) early symptomatic knee and/or hip OA. Secondly, to investigate associations between biomarkers and between biomarkers and demographics to demonstrate validity of the obtained dataset and further investigate the involvement of these biomarkers in OA.

METHODS: Fourteen biomarkers (uCTX-II, uCTX-I, uNTX-I, sCOMP, sPIIANP, sCS846, sC1,2C, sOC, sPINP, sHA, sPIIINP, pLeptin, pAdiponectin, pResistin) were assessed by ELISA or RIA in CHECK (Cohort Hip and Cohort Knee), a 10-year prospective cohort of 1002 individuals with early symptomatic knee and/or hip OA. Associations between biomarkers and demographics (age, gender, BMI, and/or menopausal status) were investigated by linear regression. Principal component analysis was performed to enable identification of clusters of interrelated biomarkers. The optimum number of clusters was determined on the basis of 'eigenvalues' and the according screeplot. The analysis was performed in all subjects together (primary analysis), but also in subjects with and without radiographic knee and/or hip OA separately (OA defined as Kellgren & Lawrence grade $\geq$1).

RESULTS: Quality controls revealed that gathered data were technically reliable. The majority of biomarkers showed relevant associations with demographic variables, which were expectedly different between genders and/or menopausal status for some. Notably, not only biomarkers of bone metabolism, but also uCTX-II showed increased levels in postmenopausal women as compared to premenopausal women and men.
Principal component analysis enabled identification of five clusters, consecutively designated as 'bone-CTX-II', 'inflammation', 'synovium', 'C1,2C-adipokines', and 'cartilage synthesis' cluster. Notably, uCTX-II clustered with biomarkers of bone metabolism, while sCOMP clustered with biomarkers of synovial activity. The adipokines loaded onto the 'inflammation' cluster and the 'C12C-adipokine' cluster.
Clusters were comparable between subjects with and without radiographic OA, except that uCTX-II showed somewhat more associations with the 'cartilage synthesis' and 'inflammation' clusters in addition to its association with the 'bone' cluster in subjects with radiographic OA as compared to those without.

CONCLUSION: The identified clusters extended knowledge on individual biomarkers from mostly smaller studies as did the observed associations between biomarker levels and demographics, from which validity of our data was deduced. uCTX-II may not only be a marker of cartilage but also bone degradation, especially in (very) early-stage OA, and sCOMP may reflect synovial rather than cartilage metabolism. Major involvement of adipokines in joint metabolism could not be identified.

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TIBIAL COVERAGE, MENISCUS POSITION AND SIZE, AND MENISCUS DAMAGE IN CONTRA-LATERAL KNEES WITH AND WITHOUT JOINT SPACE NARROWING - DATA FROM THE OAI

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INTRODUCTION: Meniscal damage (signal intensity change, tears and maceration) are common and more frequent in radiographic OA (ROA) than in non-ROA knees. Meniscal damage may cause extrusion, likely associated with less coverage and mechanical protection of the knee cartilage. However, the magnitude of tibial plateau coverage by the meniscus at different ROA grades, specifically for different JSN grades, has not been reported.

OBJECTIVE: To compare quantitative measures of tibial plateau coverage, meniscus position, and size between medial JSN (mJSN) and contralateral no-mJSN knees, using a between-knee, within-person study design.

METHODS: The subsample (n=61 persons) was drawn from the first half (2678 cases) of the OAI cohort (clinical data 0.2.1; imaging data 0.C.1). Inclusion criteria were: BMI >25, frequent knee pain in both knees; OARSI mJSN grades 1-3 in one knee, no mJSN in the contra-lateral knee, no lateral JSN in either knee. Manual segmentation of the tibial plateaus and the menisci were performed on coronal reconstructions of sagittal 3D DESSwe 3T MRI. 3D measures of meniscus position (% tibial plateau coverage, % extrusion of the tibial meniscus area, mean extrusion distance in the central 5 slices) and size (volume, height, width) were determined using custom software. Semi-quantitative scores of the menisci were read using sagittal and coronal IW-TSE 3T MRI sequences, using the MOAKS system. Differences between (contra-lateral) knees were assessed using paired t-tests, with $p<0.01$ chosen in view of multiple comparisons.

RESULTS: There were 43 grade1, 15 grade2, and 3 grade3 mJSN knees. mJSN knees showed significantly ($p<0.01$) less medial tibial plateau coverage (35.5±8.7% in mJSN1, and 29.1±11.2% in mJSN2/3 knees) than contra-lateral no-mJSN knees (45.0±7.7%). mJSN knees had a significantly ($p<0.01$) greater central extrusion distance of the medial meniscus (mJSN1: 3.1±1.8mm; mJSN 2/3: 4.2±1.8 mm) than no-mJSN knees (1.9±1.4mm), and a greater total extrusion area (data not shown). mJSN knees sowed a significantly ($p<0.01$) smaller medial meniscus width, but no significant differences were observed in volume or height. No significant differences for the lateral meniscus were seen between mJSN and contra-lateral no-mJSN knees. Of the grade2/3 mJSN knees, all had “any” medial meniscal damage, and 50% had partial or complete maceration (MOAKS≥6, maximum score in 3 regions). Of the grade1 mJSN knees, 86% had meniscal damage and 30% maceration; of the grade0-mJSN knees 69% had damage and 8% maceration. 78% of the grade2/3 mJSN knees had medial meniscus extrusion≥3mm (MOAKS grade ≥2), and 39% >5mm (MOAKS grade3). 49% of the grade1 mJSN knees had ≥3mm extrusion and 14% >5mm, whereas of the contra-lateral no-mJSN knees only 25% had ≥3mm and 3% >5mm medial meniscus extrusion.

CONCLUSIONS: In knees with frequent knee pain, meniscal damage and extrusion increase, and tibal plateau coverage decreases with increasing JSN grades. The smaller tibial plateau coverage likely involves less mechanical protection of the medial tibial cartilage in ROA knees with medial JSN.

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EFFECTIVENESS OF HYALURONIC ACID IN KNEE OSTEOARTHRITIS PATIENTS EVALUATED USING DELAYED GADOLINIUM-ENHANCED MRI OF CARTILAGE

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INTRODUCTION: Intra-articular viscosupplementation with hyaluronic acid (HA) of OA knee joints has a well-established, but temporarily positive effect on patient symptoms. The working mechanism of HA is debated and not clear yet. It has been suggested that HA might improve cartilage quality because of its potentially beneficial effect on GAG content of cartilage. Recently, we showed that dGEMRIC is a highly reproducible measure of cartilage quality in the knee in longitudinal research in early-stage OA patients.
OBJECTIVE: This study assessed if improvement in knee cartilage quality can be detected with dGEMRIC in early-stage OA knees four months after HA.
METHODS: In 18 patients with early-stage knee OA, before and four months after HA of the knee, dGEMRIC was acquired at 3T using a 3D SPGR sequenced. To evaluate patient symptoms, the knee injury and osteoarthritis outcome score (KOOS) questionnaire was also recorded at baseline and follow-up. To correct for patient motion during acquisition, both scans were registered in 3D. Next, both scans were registered to each other to enable comparison of matching cartilage regions (ROIs). We analyzed eight matching anatomical ROIs in the medial and lateral tibiofemoral knee compartment in both scans. In each ROI, the mean $T1_{GD}$ relaxation time was calculated as a measure of cartilage quality before and four months after HA. Outcomes of dGEMRIC and KOOS at baseline and follow-up were compared using paired testing to evaluate the symptomatic and potential structural effects of HA.
RESULTS: Outcomes of dGEMRIC and hence cartilage quality four months after HA did not improve significantly compared to before HA in any of the analyzed anatomical cartilage ROIs (figure 1A). However, except for the subscale 'symptoms', all KOOS subscales improved significantly after HA (figure 1B).
CONCLUSION: Outcomes of dGEMRIC indicate that, four months after HA, no improvement in articular cartilage quality is detectable in early-stage OA knees. However, similar to previous research, patient complaints decreased significantly after HA. The results of this study suggest that the working mechanism of HA is not acting through an improvement of GAG content in the cartilage.

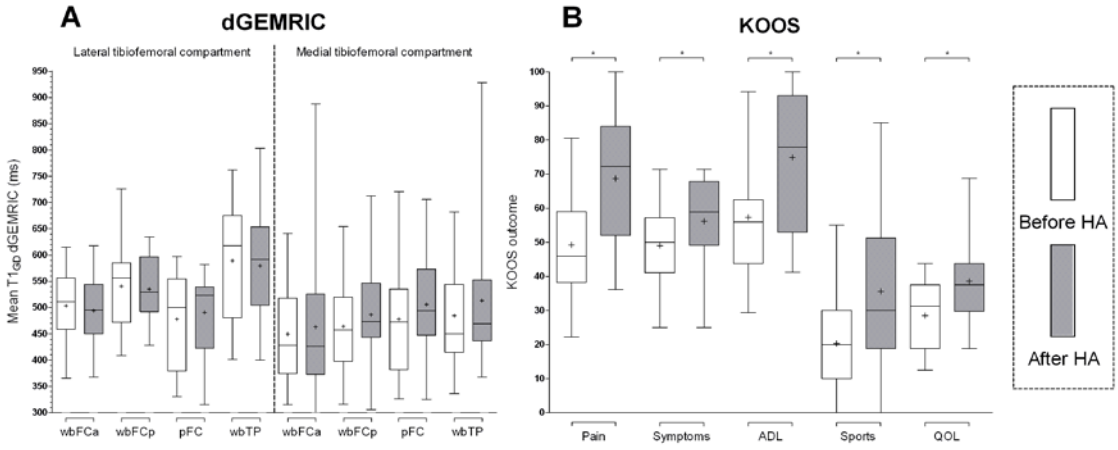

Figure 1 A: dGEMRIC outcome in each ROI before (white box) and after (grey box) hyaluronic acid. **B:** KOOS outcomes per subscale before (white box) and after (grey box) hyaluronic acid. ADL: daily activities, QOL: quality of life. Boxes range from 25th to 75th percentile, whiskers run from min to max, the horizontal line in the box represents the median, the plus sign shows the mean, *: $p < 0.05$

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P-7

PATELLOFEMORAL FRICTION SYNDROME: BIOCHEMICAL CARTILAGE IMAGING USING T2 MAPPING

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INTRODUCTION: Lateral patellofemoral friction syndrome (PFS) has been described in MRIs of patients demonstrating edema-like signal within the superolateral infrapatellar (Hoffa) fat pad. Whether this places patellofemoral cartilage at risk is unknown.

OBJECTIVE: We investigated whether patellofemoral biochemical cartilage changes would be associated with findings seen in PFS.

METHODS: In this IRB-approved retrospective study of 510 consecutive patients, 50 patients with normal or low-grade patellofemoral cartilage abnormalities (WORMS score 2 or less) were included. 22 patients with PFS (cases) were compared with an age- and gender-matched cohort of 28 patients without PFS (controls). 3T MRI was performed including multi-echo turbo-spin echo T2 (TR = 1650 ms, TE = 12.9. 25.8, 38.7, 51.6, 64.5, and 77.4 ms). Two readers independently measured bulk cartilage T2 maps in the lateral and medial patella and trochlea, and central medial and lateral femoral condyles (4 medial femur measurements were excluded because of grade 5 defects). Interobserver variability was quantified using intraclass correlation coefficients (ICC). Demographic differences and mean T2 map values were compared between cases and controls using Fisher's exact test and Wilcoxon rank-sum.

RESULTS: Interobserver agreement was good across regions between the 2 readers (ICC range 0.68 to 0.90). Patients with PFS demonstrated a higher medial patellar bulk T2 (38.1 $\pm$ 7.5 ms) vs controls (33.6 $\pm$ 7.3 ms) (p=0.03, Wilcoxon Rank-Sum). There was no significant difference between cases and controls in bulk T2 values in the lateral patella, medial or lateral trochlea, or medial or lateral femoral condyles.

CONCLUSION: T2 mapping in patients with PFS demonstrates biochemical differences in cartilage values only in the patellofemoral compartment compared to patients without edema. This may represent collagen orientation alteration in early chondromalacia (softening), possibly related to altered contact pressures. These findings should be correlated with dynamic-kinematic imaging for maltracking, and validated with longitudinal cohorts.

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P-8

FREQUENCY OF MRI-DETECTED CARTILAGE DAMAGE, OSTEOPHYTES, SUBCHONDRAL CYSTS AND BONE ATTRITION IN PAINFUL HIPS AND THE DIAGNOSTIC PERFORMANCE OF RADIOGRAPHY USING MRI AS THE REFERENCE

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INTRODUCTION: For decades, conventional radiography has been the standard imaging tool to diagnose and grade the severity of hip OA. However, radiography cannot visualize the bone marrow, cartilage and articular soft tissues that are relevant for clinical manifestation and structural progression of disease. The Hip Osteoarthritis MRI Scoring System (HOAMS) was recently developed to enable MRI-based whole-organ semiquantitative assessment of the hip joint. Frequency distribution of OA-associated features in the various anatomical subregions of the hip has not been described before. Further, the diagnostic performance of radiography to detect these abnormalities is unknown.

PURPOSE: To describe the frequencies of MRI-detected features of hip OA, i.e. cartilage damage, subchondral cysts, osteophytes and attrition, in various subregions of the hip joint and to evaluate the diagnostic performance of radiography for detection of these features using MRI as the reference.

METHOD AND MATERIALS: 52 consecutive patients with chronic hip pain (mean age ±SD 63.5±9.5 years; 54% women) without inflammatory arthritis or recent trauma were imaged by 1.5T MRI. Of these, 44 subjects (85%) underwent weight-bearing antero-posterior pelvic radiography. For MRI assessment, the hip joint was subdivided into the following subregions (modified HOAMS system): latero-superior, centro-medial, anterior and posterior. According to HOAMS, cartilage was graded 0 to 4 based on depth and area extent of surface damage. Subchondral cysts and osteophytes were graded 0-3 and 0-4, respectively based on size. Bone attrition was noted as absent or present in the latero-superior subregion only. Presence of radiographic joint space narrowing (JSN) was compared to MRI-assessed cartilage damage. Sensitivity and specificity of radiography for diagnosing each feature (presence or absence) were calculated using MRI as the reference standard, and the AUC was calculated from the ROC curve for each feature.

RESULTS: 21 of 44 subjects had radiographic OA. Frequency of diffuse cartilage damage (for n=44) (HOAMS grade 3-4) in the latero-superior, centro-medial, anterior and posterior subregions was 58%, 58%, 35% and 33%, respectively. Frequency of subchondral cysts (grade≥1) and osteophytes (grade≥1) was 31% and 64% in the latero-superior, 12% and 77% in the centro-medial, 27% and 15% in the anterior, 8% and 35% in the posterior subregions, respectively. Frequency of bone attrition in the latero-superior subregion was 17%. Sensitivity, specificity and AUC of radiography to detect MRI assessed cartilage damage were 64%, 88% and 0.76 for JSN, 84%, 71% and 0.78 for osteophytes, 44%, 89% and 0.67 for subchondral cyst, and 78%, 86% and 0.82 for attrition.

CONCLUSION: In this cohort of subjects with hip pain diffuse cartilage damage and osteophytes were more frequent in the latero-superior and centro-medial subregions, while subchondral cysts were more frequent in the latero-superior and anterior subregions. Radiography offers acceptable diagnostic performance for attrition, diffuse cartilage damage (in the form of joint space narrowing) and osteophytes, but shows low sensitivity in detecting acetabular subchondral cysts a finding explained by the projectional drawbacks of radiography.

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READER EXPERIENCE IS AN IMPORTANT FACTOR FOR SEMIQUANTITATIVE ASSESSMENT OF KNEE OSTEOARTHRITIS FEATURES BY TOMOSYNTHESIS; COMPARISON OF RELIABILITY IN READERS WITH DIFFERENT LEVELS OF EXPERIENCE

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INTRODUCTION: Digital tomosynthesis (TS) has previously been shown to offer increased sensitivity for osteophyte and subchondral cyst detection in knee osteoarthritis (OA) compared to conventional antero-posterior knee radiography (XR) when read by an experienced observer.[1] Reader experience has been shown to be an important factor to achieve high reliability for radiographic assessment of knee OA features.[2] Despite showing higher sensitivity in detecting osteophytes and subchondral cysts it is unknown whether this increased sensitivity is observer-related or a method-inherent advantage over XR.

OBJECTIVE: Aim was to compare intra- and inter-reader reliability for semiquantitative assessment of osteophytes and subchondral cysts between TS and XR among readers with various levels of expertise.

METHODS: 40 subjects (aged >40 years with or without knee pain) had both knees imaged by XR and TS. Three readers individually assessed these 80 knees: A, an expert musculoskeletal radiologist with 13 years of experience in radiographic SQ scoring of OA features; B, a board-certified radiologist with 1 year of experience in SQ scoring after training and validation, and 5 years of clinical training; and C, a 1st year radiology resident who received training on SQ scoring for the purpose of this study only, with no other experience in SQ scoring. All readers scored osteophytes based on the OARSI atlas from 0 to 3, and noted the presence or absence of subchondral cysts in four locations of the tibiofemoral joint (medial/lateral femur and tibia), using both XR and TS. 20 knees were randomly selected and re-read >1 month after the first reading. The intra- and inter-reader reliability were assessed across the knee by calculating the overall exact % agreement and the kappa (κ), which was weighted for graded scoring.

RESULTS: On XR, readers A, B and C detected 150, 131 and 112 osteophytes and 15, 13, and 19 cysts, respectively. On TS, three readers detected 178, 167 and 127 osteophytes, and 31, 28, and 37 cysts, respectively. Reader A had very high intra-reader reliability for osteophytes on both modalities (XR, 95% agreement, κ 0.96 [0.89-1.00]; TS, 100%, κ 1.00 [1.00-1.00]) and cysts (XR, 95%, κ 0.86 [0.66-1.00]; TS, 90%, κ 0.86 [0.65-1.00]). Reader B had lower intra-reader reliability than reader A, but reliability for TS was superior to XR for both osteophytes (XR, 70%, κ 0.78 [0.63-0.94]; TS, 90%, κ 0.93 [0.83-1.00]) and cysts (XR, 95%, κ 0.77 [0.35-1.00]; TS, 95%, κ 0.83 [0.50-1.00]). For reader C, TS showed higher reliability than XR for cyst evaluation (XR, 90%, κ 0.61 [0.11-1.00]; TS, 100%, κ 1.00 [1.00-1.00]) but not for osteophytes (XR, 90%, κ 0.93 [0.83-1.00]; TS, 75%, κ 0.79 [0.61-0.96]). Inter-reader reliability among three readers was similar for cysts between XR and TS (XR, 80%, κ 0.60 [0.48-0.73]; TS, 81%, κ 0.67 [0.54-0.79]) but for osteophytes it was higher for XR than TS (XR, 58%, κ 0.59 [0.52-0.67]; TS, 48%, κ 0.51 [0.43-0.58]).

CONCLUSION: TS seems to offer high intra-reader reliability regardless of the reader experience for subchondral cyst scoring. However, only the expert reader could achieve consistently high intra-reader reliability for both features on XR and TS. To optimize reliability for SQ assessment of osteophytes and cysts in the knee using TS, experience, training and calibration are important despite the higher sensitivity of TS for detection of these features in comparison to XR.

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MRI-detected subchondral bone marrow sclerosis does not predict cartilage loss in a cohort of subjects with knee pain: a 3-year follow-up study

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Introduction: The role of subchondral bone marrow sclerosis (SS) in regard to adjacent cartilage in the knee, independently of the presence of edema-like bone marrow lesions (BMLs), is not known. Histologically, subchondral BMLs and SS exhibit similar features.

Objective: To assess the association of MRI-detected SS with cartilage loss over time in the same region of the knee in a cohort of subjects with knee pain.

Methods: 163 subjects (1 knee per subject) with knee pain were included. Subjects had baseline (BL) knee radiographs as well as BL and 3-year follow-up MRIs. The knee was divided in 6 regions: patella, trochlea, medial femur, lateral femur, medial tibia, and lateral tibia. BL MRI-detected SS, defined as low-signal intensity abnormalities in the subchondral bone in both T1-weighted and T2-weighted sequences, were graded in each region from 0 to 3. Cartilage morphology was assessed in each region from 0 to 4. Grades 0 (normal) and 1 (intrasubstance signal changes) represented normal cartilage morphology. The association of BL SS with cartilage loss over time in the same region was assessed using logistic regression, adjusted for baseline age, gender, body mass index, and Kellgren-Lawrence grade in the first model, and with the addition of presence at BL of concomitant BMLs in a second model. We also assessed the correlations between radiographic and MRI-detected SS in the 3 compartments of the knee using the Spearman's rank correlation.

Results: Sixty-four (39.3%) subjects had radiographic osteoarthritis (OA) at BL. The prevalence of BL MRI-detected SS in regions varied between 1.6% (trochlea) and 17% (medial tibia). Cartilage loss over time in regions varied between 6.0% (lateral tibia) and 13.1% (medial femur). In both models we found no significant association between BL MRI-detected SS and cartilage loss. Correlations between MRI-detected and radiographic-detected SS were moderate at the medial (0.58; $p<0.001$) and lateral (0.61; $p<0.001$) compartments. In the patello-femoral compartment, correlation was 0.26 ($p<0.001$).

Conclusion: Subchondral sclerosis was not associated with an increased risk of cartilage loss in the same region of the knee after 3 years. Unlike subchondral BMLs, subchondral sclerosis may not be involved in progressive disease when cartilage loss is the outcome.

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Disclosure Statement: M.D. Crema, F.W. Roemer, M.D. Marra, and A. Guermazi (CEO) are partners of Boston Imaging Core Lab (BICL), LLC. A. Guermazi is a consultant with AstraZeneca, Novartis, Genzyme, Merck Serono, and Striker. None of the other authors declare any conflict of interest.

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ULTRA-HIGH-FIELD MRI FOR IMPROVING THE ASSESSMENT OF OSTEOARTHRITIS

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INTRODUCTION: Ultra-high-field MRI systems have several advantages over conventional 1.5T systems. Increased SNR available at higher field can be translated into increases in spatial resolution or reductions in scan time. The systems also provide higher achievable spectral resolution, and the ability to perform multi-nuclear imaging. This study uses a commercial small animal horizontal bore 7T MRI system (Bruker BioSpec^{TM}), with a bore diameter (after insertion of the radio-frequency coil) of 15.4 cm diameter, which is sufficient to accommodate a human hand for imaging.

OBJECTIVE: To perform a proof-of-principle study to (1) develop an imaging protocol optimized for the human hand, (2) evaluate image quality on realistic test objects, and (3) develop morphometric techniques for unique and improved analyses of imaging data.

METHODS: Excised chicken wings were selected for protocol development and testing because of their resemblance to human hand anatomy. MRI scan parameters were optimized in the following sequences: (1) fat-suppressed and non-fat-suppressed T1-weighted imaging (MDEFT, TR/TE 3213/3.4 ms, echo spacing 10.65 ms), (2) fat-suppressed T2-weighted imaging (3D RARE, TR/TE 7600/14 ms, rare factor: 8), (3) diffusion weighted imaging (DWIEPI, TR/TE 7500/46 ms, six A0 images), and (4) ultra-short TE imaging (UTE3D, TR/TE: 15/0.2 ms). All sequences were set up to provide isotropic spatial resolution of 0.5 mm. Image were assessed for the quality of the depiction of anatomical features of the joints between the humerus and the radius/ulna and between the radius/ultra and the metatarsals. The contrast between fluids and soft tissue components was also evaluated. Specific absorption rate (SAR) calculations for the human hand were carried out for each of the optimized sequences to insure compliance with FDA guidelines. Morphometric change analysis based on semi-automated image segmentation of bones was carried out to characterize quantitative repeatability and repositioning error.

RESULTS: The overall quality of the T1-weighted and T2-weighted images obtained with the 7T MRI system was consistent with that reported in the published literature at 7T. The diffusion-weighted images showed contrast at selected joints and regions of fluid accumulation. The UTE images revealed the short TE components of ligaments, tendons, cartilage and cortical bone. The overall reproducibility for the radius and ulnar volume was within 5% of the original volume in spite of repositioning the object in the FOV. The SAR associated with the designed protocol for the hand was *de minimis* compared to FDA limits for clinical MRI systems.

CONCLUSION: Imaging performance obtained from the Bruker BioSpec^{TM} 7T MRI system for fluids, tendons, cartilage, and bone in chicken tissue was deemed adequate for initiation of a human study. An application to the UC Davis Institutional Review Board has been submitted at the time of this writing with a research plan of scanning 15 OA patients and 15 age- and gender-matched healthy volunteers.

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FINGER LENGTH RATIOS RELATE TO HAND JOINT SPACE WIDTH IN FEMALES: DATA FROM THE OSTEOARTHRITIS INITIATIVE.

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INTRODUCTION: Previous studies have shown an association between smaller second digit:fourth digit (2D:4D) finger length ratios, viewed as an indicator of exposure to sex hormones during fetal development, and hand OA in females. However, these studies used digit length assessments that included the joint space. These assessments may be influenced by reverse causation due to the impact of joint space narrowing.

OBJECTIVE: Our aim was to explore the relationship between 2D:4D ratios, based on bone length measurements, and mean hand JSW.

METHODS: This was a secondary analysis of a pooled case-control study among participants in the OAI. Participants were included if they had hand radiographs at the baseline and 48-month visit. Two readers used a semi-automated, custom software to delineate the joint margins of the metacarpophalangeal (MCP), proximal interphalangeal (PIP), and distal interphalangeal (DIP) joints on the dominant hand. The software divided each joint into 5 regions to derive a region-specific JSW measurement (inter-tester ICC [2,1 model] = 0.82 to 0.92). Mean hand JSW was averaged across regions and fingers to calculate mean DIP JSW, mean PIP JSW, mean MCP JSW, mean JSW of digits 2 and 4, as well as a composite hand JSW measurement. One reader (intra-tester ICCs [3,1 model] > 0.99) then marked the midpoint of the base of the metacarpals and midpoint of the distal apex of the distal phalanges. The software then generated bisecting lines to measure the lengths of the metacarpals and phalanges of the second and fourth digits. Digit lengths were calculated as the sum of the distal phalanx, middle phalanx, proximal phalanx, and metacarpal lengths. The 2D:4D ratio was calculated as the second digit length divided by the fourth digit length. Previous research suggests that 2D:4D ratios differ by gender, therefore our primary analyses were stratified by gender. We used multiple linear regression models to determine the association between 2D:4D ratios and mean hand JSW, mean MCP JSW, mean PIP JSW and mean DIP JSW. For all analyses mean hand JSW was the outcome. Height and weight were included as covariates.

RESULTS: Of the initial cohort of 276 participants, 220 had readable hand radiographs. Participants were 62.6±8.5 years of age, had a body mass index of 29.6±4.6 kg/m^2, 70% female and 11 (5%) were left handed, 63 participants were from the incidence cohort. We found a significant inverse association between 2D:4D ratios and mean hand JSW among females (See Table).

CONCLUSIONS: Greater 2D:4D ratios, based solely on bone length, were related to less hand JSW in females which is discordant with previous studies that have assessed the relationship between 2D:4D ratios and hand osteoarthritis.

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DISCLOSURE STATEMENT: none.
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Table. Associations between Mean Hand JSW Measures and 2D:4D Ratio

	Males (n = 66)		Females (n = 154)	
Outcome	R^2	Beta (standard error)	R^2	Beta (standard error)
Mean Hand JSW	0.02	0.01 (1.03)	0.11	- 2.21 (0.69)*
Mean 2nd and 4th Digit JSW	0.02	0.29 (1.03)	0.11	**-2.41 (0.70)***
Mean DIP JSW	0.04	1.44 (1.14)	0.09	**-2.11 (0.76)***
Mean PIP JSW	0.02	-1.39 (1.17)	0.07	**-2.04 (0.72)***
Mean MCP JSW	0.09	-0.13 (1.46)	0.11	**-2.57 (0.93)***

*p<0.05; all models adjusted for weight and height.

P-13

VALIDATION OF THREE DIMENSIONAL DUAL-ECHO STEADY STATE SEQUENCE ON 3T MR IMAGING FOR GRADING FOCAL AND DIFFUSE ARTICULAR CARTILAGE LESIONS OF THE KNEE JOINT AS CORRELATED WITH ARTHROSCOPY

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INTRODUCTION: Cartilage imaging using the three dimensional DESS (3D DESS) technique has many advantages including; higher SNR, thinner slice thickness on 3T MR imaging, increased cartilage to fluid contrast, and isotropic resolution, which helps to reduce partial volume effects.

OBJECTIVE: The aims of our study are- 1) To correlate the grading of focal and diffuse articular cartilage lesions of the knee joint on 3D DESS with arthroscopy and 2) To test the interobserver reliability for grading articular cartilage of the knee joint on 3D DESS sequence.

METHODS: In this IRB approved retrospective study, 29 patients (mean age 39 years, SD ± 13 years) who had their knee arthroscopy performed within 3 months of 3T MR Imaging were included. Two trained musculoskeletal radiologists blinded to the arthroscopic results evaluated focal and diffuse articular cartilage lesions of the knee and graded them according to International Cartilage Repair Society (ICRS) scoring system on 3D-DESS sequence (axial, sagittal and coronal plane with 1 mm thickness). Sensitivity, specificity and accuracy were calculated with arthroscopy findings as the reference standard. Inter-observer reliability was determined with weighted kappa.

RESULTS: For focal cartilage lesions, sensitivity, specificity, accuracy for reader 1 were 55% (CI- 39%-71%), 93% (CI- 89%-96%), 88% (CI- 83%-91%) and for reader 2 were 65% (CI- 50%-79%), 84% (CI- 79%-89%), 81% (CI- 76%-86%), respectively. For diffuse cartilage lesions, the respective values for reader 1 were 61% (CI- 45%-76%), 81% (CI- 76%-87%), 78% (CI- 73%-83%) and reader 2 were 60% (CI- 45%-76%), 81% (CI- 75%-87%), 77% (CI- 72%-83%). There was fair agreement between the two readers, weighted-kappa 0.39 (CI- 0.26-0.52) for focal lesions and 0.33 (CI- 0.21-0.45) for diffuse lesions.

CONCLUSION: 3D-DESS sequence shows moderate to good accuracy, high specificity and fair reliability in diagnosis of focal and diffuse articular cartilage lesions of the knee joint. 3D DESS can be used to grade the articular cartilage lesions of the knee as an alternative 3D isotropic sequence.

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A NEW METHOD TO MEASURE ANATOMIC KNEE ALIGNMENT: A TOOL FOR LARGE STUDIES OF OA

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INTRODUCTION: Knee malalignment alters load distribution across the articular surface and is a potent predictor of knee osteoarthritis (OA) progression. The hip-knee-ankle angle (HKA) provides the most direct measurement of biomechanical leg alignment, but requires a long-limb radiograph. The femorotibial alignment angle (FTA) of the knee joint is an indirect measure of mechanical alignment and can be performed using a standard knee radiograph. Traditional methods of measuring the FTA require a reader to identify landmarks in the tibial spines, which can be difficult and unreliable for abnormally positioned knee images.

OBJECTIVE: We have developed and validated a new software method to rapidly determine FTA that may expedite the measurement of knee radiographs from large studies such as the Osteoarthritis Initiative (OAI).

METHODS: The study used 142 subjects from the Progression Cohort of the Osteoarthritis Initiative (OAI) (OAI Datasets 0.1.1, 0.B.1, and 1.B.1) where HKA measurements were available from the OAI. We excluded images where the center of the knee was less than 10 cm from the lower edge of the image. The method is a 3D extension of the coordinate system developed for location specific joint space width (JSW) measurements, previously used to improve radiographic joint space width measures. The coordinate system directly determines the orientation of the femur and also defines a central point of the knee. The axis is perpendicular to a line tangent to the base of the femoral condyles, and centered between the outer aspects of the condyles. Four points on margins of the tibial shaft define the axis of the tibia; two points are marked 10 cm from the center point and two are placed 1 cm from the base of the tibial plateau. The study used two readers. Reader 1 read the data twice with the new procedure and two times using a traditional method. Reader 2 performed a single reading with each of the two methods. Linear regression analysis was used to assess reader reproducibility, and correlation with the HKA measurement.

RESULTS: Table 1 provides the results comparing the two methods. The additional reader time was less than 30 seconds per image once an image had been processed for the location-specific JSW measurement.

CONCLUSIONS: We found improved inter and intra reader reproducibility compared with the traditional method and higher correlation with the HKA. With the new method, very little difference was observed between the inter and intra reader precision suggesting a robust technique. The fast reader time implies that assessment of large numbers of subjects is feasible. Furthermore, the method does not require landmarks placed in the tibial spines; it can be performed by a relatively unskilled reader whose task is limited to marking points on the shaft of the tibia and the femoral condyles. A limitation of the method is that it relies on the coordinate system set up for location specific JSW; additional time is necessary if this step has not already been performed. However, setting up the coordinate system is substantially automated and could be performed independent of measuring JSW if necessary. In summary, we have documented a new technique that can provide a precise, accurate, rapid and reproducible measurement of radiographic knee anatomic alignment, with significant implications for efficiency and cost-effectiveness for very large studies of knee OA.

	Intra-reader	Inter-reader	Correlation with HKA
Traditional Method	0.92	0.85	0.46
New Method	0.97	0.96	0.51

Table 1. R squared values from a linear regression fit.

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A RAPID, NOVEL, QUANTITATIVE METHOD FOR MEASURING MRI-DETECTED BONE MARROW LESIONS IN KNEE OSTEOARTHRITIS IS COMPARABLE TO WORMS

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INTRODUCTION: Imaging methods that rapidly, economically and accurately detect and measure BML are important in large OA studies such as the OAI which contains over 38,000 individual TSE IM MRI scans (baseline to 48 month).

OBJECTIVE: To compare a novel semi-automated method to measure BML volume quantitatively with BML assessment from the Whole-Organ Magnetic Resonance Imaging Score (WORMS).

METHODS: The sample were n=115 subjects from the baseline data of the OAI Progression Cohort (Image Releases 0.B.1, 1.B.1) whose knees had been WORMS-scored by OAI central imaging. Sagittal turbo spin echo fat saturated 3T (TSE FS) IM MRI were obtained. A reader (CR) used semi-automated software to segment the subchondral BMLs in the distal femur. The software applies a grayscale thresholding algorithm to the raw image and provides the reader with regions for potential segmentation. With 1 or 2 mouse clicks, the reader selects clinically appropriate region(s) of BML. The primary outcome was total segmented volume of BMLs in the femoral medial and lateral compartments, based on number of voxels highlighted. Comparison of compartment BML volume was made with public-release WORMS scoring for the medial and lateral compartments (summed score across anterior, central and posterior, sub-regions). To assess intra-rater and inter-rater reliability 20 scans were scored two times by one reader (CR) and by an experienced radiologist (CV). Descriptive statistics, Spearman's correlation and the Kruskall-Wallis test were used to assess association between the two methods. ICC's were calculated for reliability.

RESULTS: The software method required an average of 3 minutes per knee. The mean (SD) of BML volume was 429.7 mm^3 (593.4) and 132.1 mm^3 (224.3) for lateral and medial compartment respectively. Significant positive associations with WORMS score were found in both medial and lateral compartments ($p<0.001$). Spearman's correlation between volume and WORMS score 0.85 ($p<.0001$) for both medial and lateral compartment. ICC's for intra and inter-rater reliability were 0.96 and 0.97 respectively.

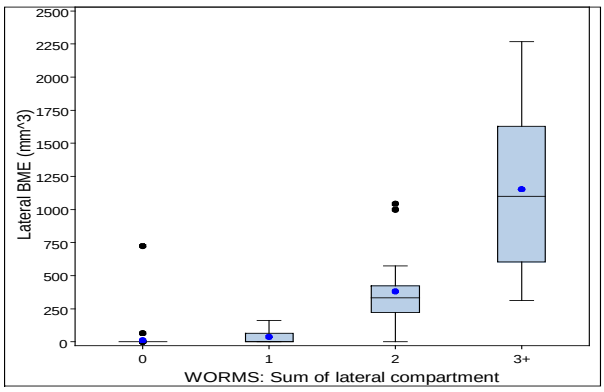

Figure 1 Volumes of BML vs. WORMS categories for the lateral femur (summed score across ant, central and posterior, sub-regions; capped at 3).

CONCLUSION: We have documented a fast, semi-automated software method to segment BML in knee OA subjects using 3T TSE FS MRI that could potentially be a surrogate for WORMS scoring. Using this method, it is feasible to assess a large number of knees in a short period of time.

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DICLOSURE STATEMENT: None
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P-16

A QUANTITATIVE METHOD FOR MEASURING MRI-DETECTED OSTEOPHYTES IN KNEE OSTEOARTHRITIS: DESCRIPTION OF A NEW METHOD FOR LARGE OA DATASETS

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INTRODUCTION: Imaging methods that rapidly, economically and accurately detect and measure osteophytes are important in large OA studies such as the OAI which contains over 38,000 individual double echo steady state (DESS) MRI scans (baseline to 48 month). Further, volumetric analysis has the potential to detect small changes in osteophyte size that may be a sensitive marker for incident or progressive OA.

OBJECTIVE: To describe a new software-based semi-automated method to measure and quantify osteophyte volume, and report reading time per knee scan

METHODS: The sample were n=20 randomly selected subjects from the baseline data of the OAI Progression Cohort. Inclusion criteria were a baseline KL grade of 2 or 3. 3T DESS MRI images were obtained. A reader (CR) identified and indexed the first and last slice on which an osteophyte appeared. The software then automatically applied an edge detection algorithm to detect and demarcate the bone edge on all slices between and including the first and last slice, and provided the reader with regions for potential segmentation (figure 1a). With 1 or 2 mouse clicks, the reader can select clinically appropriate region(s) of osteophytes by 'closing off' the contour (Figure 1b). Reading times were recorded for each knee.

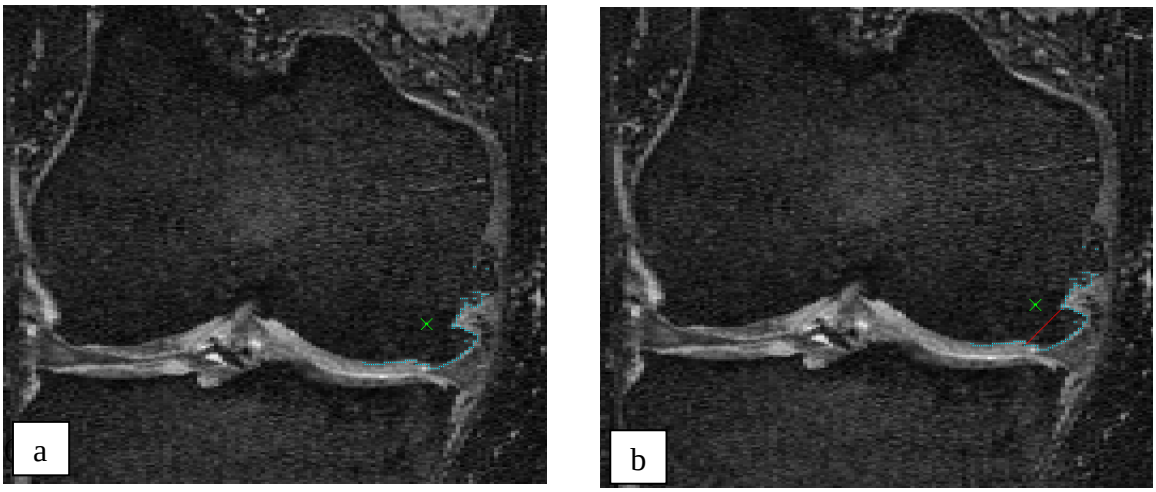

Figure 1 Osteophyte segmentation. (a) reader identifies and indexes (with 'X') first and last slice of osteophyte , software detects and demarcates bone edge on all slices from first to last (b) reader closes off OP (1 or 2 mouse clicks)

RESULTS: The software method required an average of 3 minutes per knee. Osteophytes were successfully segmented, and volumes of osteophyte in the distal femur determined.

CONCLUSION: We have described a semi-automated software method to segment osteophytes in knee OA subjects using 3T DESS FS MRI that could potentially increase accuracy of osteophyte volume measurement. Once fully validated, this method may make it feasible to assess a large number of knees in a short period of time, and offer a potentially sensitive measure of osteophyte volume.

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P-17

NON-TERMINAL ANIMAL MODEL OF EARLY OSTEOARTHRITIS

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INTRODUCTION: There is a well recognized need for a translational model of acute joint injury and early OA. Using horses as an acute injury model has a number of advantages. Athletic stresses on the joint are similar in humans and horses and the resulting OA lesions also are similar.

OBJECTIVE: The purpose of this study was to develop a non-terminal equine model that demonstrated clinical and morphological evidence of the onset and progression of OA. We hypothesized that creation of an osteochondral (OC) injury in the metacarpophalangeal (MCP) joint of the horse would result in clinical, radiographic, arthroscopic, and histologic changes characteristic of early OA.

METHODS: Twenty-two clinically and radiographically normal age- and sex-matched Quarter Horses were randomly divided into 1 of 2 groups: (1) horses (n=11) that had an OC fragment created arthroscopically on the proximal dorsomedial aspect of the first phalanx in one MCP joint and a sham operation in the contralateral joint at week 0; and (2) unoperated exercise control horses (n=11). All horses were exercised on a high-speed treadmill 5 days/week from week 2 to week 16. At week 16, OC fragments were arthroscopically removed and small synovial and cartilage biopsies were taken from OC injured and sham joints. Every 2 weeks throughout the study, force plate analysis, joint range of motion, and effusion scores were recorded on all horses and joint fluid, serum and urine were collected for future biomarker analyses. A repeated measure ANOVA with Tukey's for multiple comparison was used for analysis of clinical data. Week 0 and 16 radiographs (all horses) and arthroscopic videos (OC injured and sham joints) were blinded and graded for OA changes. Synovial membrane biopsies obtained from all OC injured joints at weeks 0 and 16 and from sham joints at weeks 0 (n=5) and 16 (n=11) were blinded and graded histologically, as were articular cartilage samples obtained from the third metacarpal bone (opposite OC fragment) at week 16 in OC injured (n=11) and sham (n=6) joints. All scoring systems except that used for cartilage were analyzed using a Kruskal-Wallis test with a Dunn's multiple comparison test; a Mann Whitney t test was used for cartilage. $P<0.05$ was considered significant. All procedures were approved by institutional animal care and use committees.

RESULTS: Osteochondral fragments were successfully created and multiple clinical and morphologic changes consistent with early OA were demonstrated. OC injured horses exhibited a decrease in forelimb symmetry ($P<0.001$) at week 2 on the force plate, indicating pain. No further differences were seen over time or between groups. By week 16, range of motion decreased in 9/11 (82%) OC injured limbs compared to no change in sham and control limbs. Subjective joint effusion scores increased in OC injured limbs compared to baseline throughout the entire study period ($P<0.001$). Radiographic scores showed subtle but significant change in the OC injured limbs ($P<0.05$). Arthroscopically, synovial membrane from OC injured joints exhibited mild changes (hyperemia, villus thickening, and proliferation). However, cartilage damage within the joint was more pronounced. Histologically, chondrocyte necrosis and proliferation (repair) were significantly greater in OC injured cartilage compared to sham cartilage ($P<0.05$), with the majority of changes restricted to the superficial zone, and a non-inflammatory fibrotic reaction was seen in OC injured synovium.

CONCLUSION: Creation of an OC fragment in the equine MCP joint resulted in acute traumatic joint injury that has mild but consistent clinical and morphological features of early OA that manifest as a superficial lesion in articular cartilage. This non-terminal injury model will be useful for defining biomarker changes of early OA and for monitoring response to therapy of this disease.

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DIFFERENCES IN HIP SHAPE AMONG AFRICAN AMERICANS AND CAUCASIANS WITHOUT HIP OA USING ACTIVE SHAPE MODELING : THE JOHNSTON COUNTY OA PROJECT

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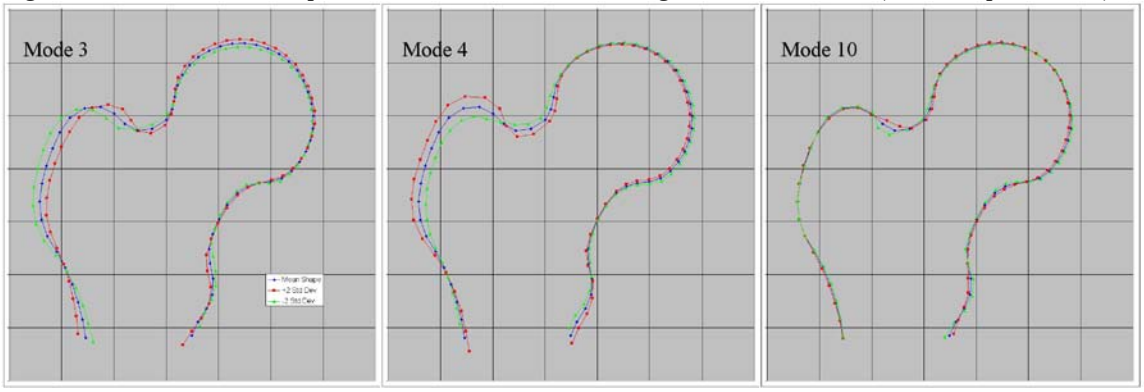
INTRODUCTION: Differences in hip shape have been identified among hips that do and do not develop incident hip OA (Lynch 09, Gregory 07). We have identified variations in individual radiographic features by race (Nelson 10), and hypothesized that hip shape by active shape modeling (ASM) may differ by race.

OBJECTIVE: To determine if there are differences in shape among hips without baseline hip OA from African American and Caucasian participants in the Johnston County OA project.

METHODS: We selected all hips developing OA from baseline (KLG 0 or 1, 1991-7) to follow up (KLG >=2, 1999-2004, mean 6 years follow up), and 1:1 control hips (KLG 0 or 1 at both baseline and follow up) from similar race and gender strata. The shape of the proximal femur was defined on a baseline AP pelvis radiograph for 617 hips by a single trained reader (AEN), and 60 landmark points (10 points between the lesser trochanter and femoral neck, 30 around the femoral head, and 20 around the greater trochanter and femoral shaft to the level opposite the lesser trochanter), were input into an ASM. The ASM produced a mean shape, plus independent modes of variation in that shape. Modes which between them explained 95% of shape variance were included in logistic regression models as independent predictors, with race as the dependent variable. Additional analyses were adjusted for sex, baseline KLG, and incident hip OA at follow up. This preliminary analysis includes 347 hips with available data from 308 individuals including 61% women and 83% Caucasians.

RESULTS: Shape variations in modes 3 , 4 and 10 (representing 13, 10, and 1% of total shape variance, respectively) were significantly associated with being African American (ORs for 1-SD <u>increase</u> in mode score-Mode 3: 1.4 [95% CI 1.0, 2.0]; Mode 4: 2.5 [95% CI 1.6, 4.0]; Mode 10: 2.1 [95% CI 1.5, 3.0], see figure). Mode 13 (0.6% total variance) was associated with an OR of 1.4 [95% CI 1.1-2.0] per 1-SD <u>decrease</u> in mode score. There was essentially no change in the estimates when adjusted for sex, baseline KLG, and incident hip OA at follow up.

<u>Figure. First 3 modes of shape variation associated with being African American (mean shape +/- 2SD)</u>



CONCLUSION: Variations in shape modes 3, 4, and 10 , derived from the ASM, were associated with being African American when compared to Caucasian participants. Such shape variations may contribute to hip OA risk or variations in pattern of hip OA by race and will be the focus of ongoing study.

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THIGH MUSCLE CROSS SECTIONAL AREAS AND STRENGTH DO NOT DISPLAY SIGNIFICANT CHANGES OVER TWO-YEARS IN EARLY OR ADVANCED PAINFUL KNEE OA

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INTRODUCTION: Knee OA has been shown to be associated with reduced quadriceps strength. Two-year changes in quadriceps muscle volume were found to be associated with age, but not with radiographic OA (ROA) vs. non-ROA status (Beattie et al. *Arthritis Care Res* 64: 2012). The current study aims to extend previous analyses to various ROA (JSN) strata, in order to elucidate the association between of knee OA and thigh muscle status, using a within-person, between-knee comparison study design.

OBJECTIVE: To determine side differences of longitudinal (2 year) changes in thigh muscle strength and anatomical thigh muscle cross-sectional areas (ACSAs) in ROA knees of OAI participants with bilateral knee pain and unilateral medial JSN (mJSN).

METHODS: 70 participants of the first half of the OAI cohort (C release; n=2678 cases) fulfilled the following inclusion criteria: BMI>25, frequent bilateral knee pain (most days in at least one month in the past 12 months), medial JSN OARSI grades 1-3 and no (or less) lateral JSN in one knee, no medial or lateral JSN in the contra-lateral knee. Baseline and follow-up axial non-fat-suppressed T1-weighted SE 3T MRIs of the thigh of 37 of these participants (age 63.4±8.9 y; BMI 31.1±4.2) and maximal isometric strength data (Good Strength Chair, Metitur Oy, Jyvaskyla, Finland) of 29 participants were available. Quadriceps, hamstrings and adductor ACSAs were segmented at 33% estimated femoral length (from distal) and single quadriceps heads at 30% (vastus medialis=VM, lateralis=VL, intermedius=VIM, rectus femoris=RF). Muscle ACSAs and signal intensity (as a potential measure of fat content) were calculated using custom software. Specific strength was calculated as strength/ACSA. Paired t-tests were used to compare the rates of change in JSN versus contra-lateral no-JSN knees, using $p<0.01$ in view of multiple comparisons. Sensitivity analyses were performed by stratifying for JSN grade 1 and 2/3.

RESULTS: There were no significant changes (at $p<0.01$) in thigh muscle ACSAs and signal (including quadriceps heads), extensor or flexor strength, or in specific strength in either the JSN or no-JSN knees over the 2 years (Table 1). Further, 2-year rates of change did not differ significantly between JSN and no-JSN knees, except for the SD (heterogeneity) of the signal intensity in the VM that increased more strongly in mJSN than in no-mJSN knees [p=0.005]). No significant 2-year changes were observed in mJSN1 or 2/3 strata, nor differences in rates of change between mJSN1 or 2/3 vs. contra-lateral no-mJSN knees.

Table 1: Mean % changes over two years (mean±SD) in no-mJSN and in mJSN painful ROA knees

	Anatomical cross-sectional area				Muscle strength		Specific strength	
	Quad.	VM	Hamst.	Adductors	Extensors	Flexors	Extensors	Flexors
Δ% no mJSN	-1.1±8	-1.8±8	-2.4±6	+2.8±21	+1.2±23	-4.6±30	+2.5±22	-2.0±28
Δ% mJSN	-1.2±8	-1.0±8	-1.0±8	+0.6±22	-3.1±37	-7.3±40	-4.3±40	-6.0±39
Δ% mJSN 1	-0.6±7	-1.8±6	-0.5±7	+2.5±25	-4.2±39	-8.7±42	-5.5±43	-7.9±39
Δ% mJSN 2/3	-2.6±10	+0.6±11	-1.9±9	-2.8±18	+1.3±21	-1.8±26	+0.4±22	+1.8±29

CONCLUSION: Our study extends previous findings (Beattie et al. *Arthritis Care Res* 64: 2012) that change in quadriceps volume is not associated with ROA status. In this small sample, no significant change in thigh muscle ACSAs and signal (including all thigh muscles and quadriceps heads) and (specific) muscle strength over 2 years in painful ROA knees, and no differences between mJSN and no-mJSN knees.

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ACKNOWLEDGMENT: This abstract has received approval by the OAI publication committee
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P-20

THE IMPACT OF MINIMUM JOINT SPACE WIDTH EXCLUSION CRITERIA ON THE SENSITIVITY TO CHANGE IN KNEE OSTEOARTHRITIS - DATA FROM THE OAI

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INTRODUCTION: Knee OA trials that have used change in minimum radiographic JSW (mJSW) in the medial femorotibial compartment (MFTC) as an outcome have commonly excluded knees below a certain baseline (BL) mJSW threshold (e.g. 2 or 3 mm). This was done to avoid a "ceiling" effect, when the mJSW approaches 0mm. However, recent MRI studies have shown that knees at advanced stages of radiographic OA (KLG 3) display a higher sensitivity to change than those with early radiographic OA (KLG 2).

OBJECTIVES: 1) To determine the sensitivity to change of radiographic and MRI-based outcomes as a function of baseline mJSW ranges, 2) to assess the impact of mJSW thresholds for subject inclusion/exclusion on cohort characteristics.

METHODS: Sensitivity to change (SRM=mean/SD change) over one year was determined in 925 OA knees (KLG 2-4; central readings) from fixed flexion radiographs (FFR) and 3T MRI (DESS or FLASH). Medial mJSW, fixed location JSW(X=0.225), MFTC cartilage thickness, and central subregional MFTC cartilage thickness (cMFTC) were used as outcomes. The impact of mJSW thresholds on cohort characteristics was studied using 3490 knees with radiographic OA from 2320 OAI participants.

RESULTS: The SRM for FFR JSW measures was greater (more negative) in knees with 1-4mm than in those with <1mm or > 4mm BL mJSW (Table 1). The greatest SRM for mJSW was observed with 2-3mm BL mJSW (-0.47), and that for fixed location JSW(X=0.225) with 1-2mm BL mJSW (-0.72). The greatest SRM for MRI measures was observed with 1-2mm BL mJSW (MFTC: -0.70, cMFTC: -0.76), but in contrast to FFR, MRI also showed high SRMs for <1mm BL mJSW. Progression to 0mm mJSW over one year was observed in <1%/14%/55% of knees with ≥2mm/1-2mm/<1mm BL mJSW. The proportion of knees with KLG 3/4 was 31%/7% for the total cohort (n=3490 knees), 29%/2% in knees with ≥2mm, 19%/3% in knees with ≥3mm, and 13%/4% in knees with ≥4mm BL mJSW The proportion of knees with lateral JSN in all KLG 3/4 knees (n=1095) was 9% without BL mJSW threshold, 10% with a ≥2mm, 11% with ≥3m, and 15% with ≥4mm BL mJSW.

Table 1: Standardized response mean (SRM) for different ranges of baseline (BL) minimum JSW (mJSW)

SRM	<1mm	1-2mm	2-3mm	3-4mm	4-5mm	≥5 mm	≥4mm	≥3mm	≥2mm	≥1mm	≥0mm
mJSW	+0.40	-0.39	-0.47	-0.39	-0.17	-0.24	-0.20	-0.27	-0.29	-0.30	-0.28
JSW(0.225)	-0.06	-0.72	-0.49	-0.49	-0.23	-0.31	-0.27	-0.34	-0.36	-0.39	-0.37
MFTC	-0.57	-0.70	-0.40	-0.38	-0.16	-0.13	-0.15	-0.23	-0.26	-0.31	-0.31
cMFTC	-0.58	-0.76	-0.52	-0.44	-0.24	-0.14	-0.19	-0.28	-0.32	-0.36	-0.37
N	29	81	139	233	238	205	443	676	815	896	925

CONCLUSION: When radiographic JSW is used as the outcome, knees with <1mm BL mJSW should be excluded to avoid ceiling effects. Generally, central fixed-location JSW is more sensitive than mJSW. From a standpoint of sensitivity to change (SRM), a BL mJSW threshold is not required when cartilage loss is measured with MRI. Thresholds of ≥2mm reduce the observed sensitivity to change for JSW and cartilage loss, because knees with earlier radiographic OA have slower structural progression than those at later stages. In addition to the inclusion of a greater proportion of KLG 2 knees, increasing mJSW thresholds for study eligibility may also lead to the inclusion of a greater proportion of KLG 3/4 knees with lateral JSN.

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AUTOMATIC MULTI-ATLAS-BASED SEGMENTATION OF CARTILAGE FROM KNEE MR IMAGES

ON JULY 12th – 14th in HILTON HEAD, SOUTH CAROLINA

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INTRODUCTION: Fully-automatic cartilage segmentation methods are needed to rapidly screen large image databases to assess changes in cartilage morphology. We therefore propose an automatic multi-atlas-based cartilage segmentation method from T1-weighted MR images.

OBJECTIVE: We address the following problems

1) Automatic multi-atlas-based bone segmentation
2) Automatic multi-atlas-based cartilage segmentation

METHODS: We propose an automatic multi-atlas-based cartilage segmentation approach. In the medical image analysis field, an atlas can be an average shape image or an individually labeled image. Multi-atlas-based methods make use of multiple labeled images as atlases. Our atlases are knee MR images with expert segmentations of femur, tibia, femoral and tibial cartilage. We demonstrate how multiple atlases can be used for cartilage segmentation through image registration.

Our overall analysis pipeline starts with a multi-atlas segmentation of the femur and tibia using the image intensity and the spatial prior obtained from multi-atlas registration. The bone segmentation allows us to automatically locate cartilage in the image. We also use local features in the joint region for a probabilistic classification of cartilage. Our cartilage segmentation is especially designed to segment touching objects such as femoral and tibial cartilage.

We tested our automatic analysis pipeline on a dataset containing 211 T1-weighted (3D SPGR) images at a resolution of $1.00 \times 0.31 \times 0.31$ mm^3. Expert cartilage segmentations were available for all images. Expert bone segmentations were available for 18 images. Within the 18 images, we tested each image using the other 17 images for training. Outside of the 18 images, we used all the 18 images for training.

RESULTS: We validated the proposed segmentation result against the expert segmentation. Bone segmentations were validated on 18 images and the cartilage segmentation were validated on 211 images. Table 1 shows the mean Dice similarity coefficient (DSC, measuring the segmentation agreement) and the standard deviation for different objects.

Table 1 Mean DSC (standard deviation).

Femoral bone	Tibial bone	Femoral cartilage	Tibial cartilage
97.3% (0.8%)	96.5% (1.1%)	73.4% (6.8%)	80.6% (5.7%)

CONCLUSION: We proposed a fully-automatic cartilage segmentation method, which is an important step towards automatic quantitative analysis of longitudinal cartilage changes.

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AN X-RAY CLASSIFICATION PROBLEM DEMONSTRATES MRI-BASED SUBREGIONAL CARTILAGE THICKNESSES PERFORM BETTER THAN AGGREGATED MEASURES

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INTRODUCTION: Via posters and presentation at the 5th IWOAI, the author suggested turning to multivariate techniques to better exploit the complex relationships among imaging covariates. Building on that sentiment, consider the medial JSN classification problem: Suppose an algorithm learns from a subset of covariates associated with medial x-ray (mJSW, osteophytes, etc., but stripped of JSN and KLG) and some core baseline covariates (gender, age and valgus/varus) about scoring medial JSN into grades 0, 1, 2, and 3. How well does the algorithm compare to the radiologist's JSN grading when presented with new patient data? Natural follow-ups include: What if the x-ray data is replaced or combined with MRI-based cartilage thickness measures? Is it better to use aggregated MRI measures or is there an advantage to using the collection of sub regional endpoints? Do findings change when JSN is swapped with 'collapsed JSN' ({0, 1}, {2, 3}), KLG or 'collapsed KLG' ({0, 1}, {2, 3}, {4}} grades?

OBJECTIVE: Two families of machine learning algorithms were studied: k-nearest neighbor (KNN) with k = {1, 3, 5, …, 13} and support vector machine (SVM) using Gaussian radial basis kernel. Two parameters, called C and sigma, uniquely identify such SVM algorithms. The questions motivated in the introduction were explored via cross-validation exercises. In total, 21 combinations of x-ray and MRI covariates, henceforth referred to as imaging covariate groups (ICGs), are considered.

METHODS: Two subsets from the OAI were used for this exercise. The first data set included 994 records for which the core baseline and median x-ray ICG data were complete. A second data set of 389 records was a subset of the former obtained by further demanding MRI ICG data were complete. In a cross validation exercise, datasets are randomly partitioned into 2 groups (70% for algorithm training, 30% for algorithm testing) and the concordance rates of the algorithms and the radiologist are collected. Conducting many cross-validation exercises on random partitions allows qualitative assessment of algorithm robustness relative to the training data sets and notions of over-fitting.

A parameter tuning exercise was first performed: 24,321 SVM algorithms over a 121 x 201 grid of parameters (C x sigma) first studied the medial JSN classification problem with the medial X-ray ICG. 7 KNN and 20 SVM algorithms (randomly chosen from the optimal parameter region) were progressed to the main investigation. For each of 4 response variables (JSN, KLG and collapsed versions), 250 partitions were used with the 27 algorithms to record concordance under 21 ICGs. Box plots and summary statistics are used to harvest results from the 4*250*27*21 = 567,000 cross-validation exercises.

RESULTS: SVM algorithms consistently outperformed KNN algorithms at producing JSN classification concordant with the radiologist. Among 21 ICGs, SVM-based classification with medial X-ray provided a benchmark, balancing concordance rate (75%) while avoiding higher variability associated with over fitting. The 8-dimensional sub regional MFTC was the runner up (63% concordance). Concordance rates improved with collapsed JSN (90%, 87%, respectively). As expected in this exercise of medial JSN classification, lateral X-ray and lateral MRI data performed the worst. When X-ray and MRI ICGs were combined, median performance generally improved, but so too did variability. For MRI-based ICGs, an advantage in classification accuracy from using collections of sub regional endpoints rather than aggregates was consistently demonstrated in MFTC, but not LFTC. Results were similar with KLG-based responses.

CONCLUSION: The final result described provides further credence to the recommendation for multivariate techniques: Information contained in the collection of MFTC sub regional cartilage thickness measures is lost when subregions are aggregated. At least two questions merit further research: 1) Is the poorer accuracy observed with MRI merely a byproduct of the smaller number of available records? 2) How well might these algorithms perform in identifying patients who ultimately progress?

SPONSOR: GlaxoSmithKline
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COMPARISON OF T1RHO IMAGING AT 3 TESLA AND 7 TESLA IN KNEE CARTILAGE

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INTRODUCTION: MR T1rho relaxation times have been used as markers for proteoglycan and collagen content in articular cartilage and elevated T1rho have been associated with the osteoarthritis. While these mechanisms have been studied extensively at 3 Tesla, very few studies have been done at 7 Tesla, particularly for T1rho. Kogan, et al. (MRM, 2011, DOI: 10.1002/mrm.23213) have studied T1rho relaxation using the proton transfer ratio, but have not performed T1rho mapping. To our knowledge, no comparisons of the T1rho relaxation time have been reported between 3T and 7T in vivo. In this work, we present T1rho results at 3T and 7T in vivo.

OBJECTIVE: T1rho measurement at 7T will provide increased SNR and sensitivity when compared to measurement at 3T.

METHODS: The 3D MAPSS sequence previously developed for T1rho imaging at 3T (Li, X, MRM, 2008:59) was implemented on a 7T GE MR scanner.

To determine the differences in field strength in vivo, the knee of a healthy volunteer (Male, Age 23) was imaged at 3T and 7T. Imaging parameters used for both scans were FOV=15cm, 256x128 matrix, slice thickness=4mm, spin lock frequency=200Hz, TSL=[0,10,15,45ms], TR/TE=5.2/2.9ms, slices=30, and parallel imaging (R=2.67). The bandwidth was doubled at 7T compared to 3T due to anticipated SAR limitations. Imaging at 3T was performed with an 8-channel knee coil (Invivo Inc., Gainesville, FL) while imaging at 7T was performed with a 28-channel knee coil (QED, Mayfield Village, OH). For all spin lock preparation pulses, 135° composite pulses were added to address B0 and B1 inhomogeneities.

RESULTS: Figure 1 shows the T1rho values of the phantoms at 3T and 7T. T1rho in vivo images at similar slices in the knee are shown in Figure 2. Mean values of T1rho in areas of the cartilage are shown in Table 1. SNR values at 3T and 7T are reported in Table 2

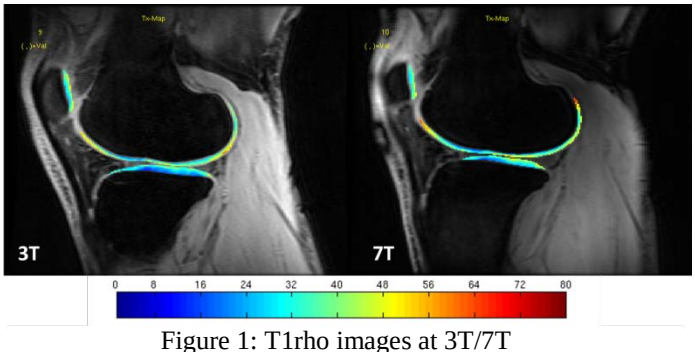

Figure 1: T1rho images at 3T/7T

Table 1: T1rho values of the cartilage		
Region	3T	7T
Patella	36.61	36.50
Femoral	38.65	38.30
Tibial	27.43	31.70

Table 2: SNR value at TSL=0		
Region	3T	7T
Patella	99.28	255.12
Central Cartilage	87.70	118.52

CONCLUSION: The 7T images display higher SNR, particularly in the patella. This was expected as the signal to noise ratio increases with field strength and the number of coil elements. However, these numbers are impressive considering the increased bandwidth used at 7T.

The results presented demonstrate the feasibility of 3D MAPSS T1rho imaging at 7T. Future work will involve imaging of additional healthy subjects at 3T and 7T, to provide statistical significance.

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P-24

DEGENERATIVE CHANGES FIVE YEARS AFTER AN ANTERIOR CRUCIATE LIGAMENT RUPTURE ASSESSED BY MOAKS

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INTRODUCTION: An ACL rupture is a well-known risk factor for the development of OA. Several studies showed that 50 – 85 % of patients with an ACL rupture had slight-to-moderate radiographic changes related to OA at 12 to 20 years after trauma. The pathophysiology of an ACL rupture leading to evident radiologic knee OA still remains largely unknown. Compared to radiography, MRI is a more sensitive tool for detecting degenerative changes and for monitoring progression of OA. Identifying early degenerative features is important for development and monitoring of early interventions. The MRI Osteoarthritis Knee Score (MOAKS) is a semi-quantitative scoring system for OA features that builds on the prior experience of other semi-quantitative scoring systems.

OBJECTIVE: To assess which OA features and degenerative changes are detectable in chronic ACL deficient knees assessed by MOAKS 5 years after initial trauma.

METHODS: Patients whom consulted an orthopaedic surgeon 5 years ago because of a complete ACL rupture, confirmed by MRI within 6 months after trauma, were eligible. Inclusion criteria for this study were non-operative treatment, age at trauma $\leq$ 45 years and no clinical signs of OA at time of trauma. Patients with previous intra-articular knee trauma and arthroscopy during follow-up period were excluded. MRI scans were acquired at 1.5T of all patients. MRI scans were evaluated by a MD researcher and an experienced musculoskeletal radiologist according to the description of MOAKS. In total we included 30 patients with the following characteristics: mean age at trauma was 33.6 years (± 7.1), 30% was female, mean pre trauma Tegner activity score was 7.3 (± 1.6) and at follow-up 5.8 (± 2.0). Fifty percent of the patients had at follow-up giving way complaints varying from few (once a year) to severe (once a week).

RESULTS: Until now, we assessed the MOAKS of 10 of 30 patients. Further assessments are ongoing. At baseline BM lesions were present in the lateral femur (40%) and tibia (60%) and medial femur (30%) and tibia (20%). At 5 years follow-up only in the lateral femur BM lesions (30 %) were present; one new and two old lesions. Articular cartilage damage was present at baseline in the following regions: lateral trochlea femur (10%), lateral central femur (70%), lateral posterior femur (10%), medial anterior tibia (10%), medial central tibia (10%) and lateral anterior tibia (20%). At follow-up the cartilage score was nearly similar. Only one new defect in the medial posterior femur region could be detected. The number of patients with osteophyte formation increased at follow-up compared to baseline in the following regions: inferior patella (40 % to 70%), medial posterior femur (30% to 100%), lateral posterior femur (30% to 80%) and central part of medial and lateral femur (both 50% to 70%). Tibial osteophytes were hardly scored and at follow-up there were no changes. At follow-up signal abnormality was scored mainly in the posterior horn of the medial (80%) and lateral (60%) meniscus. After trauma one complex and one vertical tear were determined in the anterior horn of the lateral meniscus. During the follow-up period two new meniscal tears (horizontal and complex) developed in the anterior horn of the lateral meniscus. Nearly all patients (80%) had a positive score for effusion-synovitis at baseline because of ACL trauma. At follow-up small effusion-synovitis was present in 50% of the knees and medium effusion-synovitis in 20%.

CONCLUSION: So far only small changes related to OA were detected in a population with chronic ACL rupture whom were treated non-operatively. The femur seems to show the most OA features at 5 years after an ACL rupture, namely cartilage defects and osteophytes. Besides, abnormal signal in the meniscus and effusion-synovitis were frequently scored at follow-up.

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P-25

THE USE OF MIXED EFFECTS MODELS IN ASSESSING SUBREGIONAL KNEE CARTILAGE THICKNESS CHANGE BETWEEN TREATMENT ARMS OF A CLINICAL TRIAL

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INTRODUCTION: Quantitative measures of knee cartilage thickness change (ΔThCtAB) are viewed as potential biomarkers for efficacy in clinical DMOAD trials. Cartilage thickness biomarkers have been either location based measures of change (femoro-tibial compartment, femoral/tibial plates, or plate subregions), or change based (ordered values of subregional changes). Statistical analyses typically have included multiple tests examining individual subregions separately. Mixed effects models provide an opportunity to include all subregions in a single analysis which may provide more statistical power than analysis of a single measure averaging cartilage thickness change over the same spatial area, but models are sensitive to deviation from model assumptions. Studies have shown that changes can be rapid and local in some OA subjects, while others show little or no change; hence change distributions may not meet needed model assumptions.

OBJECTIVE: To assess the use of mixed effects models to test for differences between treatment arms in the rate of change in knee cartilage thickness. Specific questions examined include

1) Are tests using mixed effects models biased?
2) Do mixed effects models provide increased sensitivity over use of univariate measures of change represented by MFTC ΔThCtAB?

METHODS: Data from a 2-year, multinational, multicenter, double-blind, parallel group DMOAD trial were used in this study. Participants with body mass index (BMI) of 25 to 40 kg/m^2 and symptomatic knee OA, i.e., KLG2 or 3 in the study knee with lateral<medial JSN, were randomly assigned to receive 0, 50 or 200 mg QD of the selective iNOS inhibitor (cindunistat/SD-6010). This study examines the subcohort that underwent coronal FLASHwe MR imaging and had cartilage thickness results for all plates (59 subjects completed 6M, 47 completed 12M, and 34 completed 24M follow-up). ΔThCtAB from medial femoro-tibial compartments, plates, and subregions were assessed by trained readers at a single analysis center (Chondrometrics, Ainring, Germany) blinded to time point and treatment group. Ordered values, subregion values of medial compartment sorted from greatest thinning to greatest thickening, were computed. Mixed effects (LME) models with KLG and Treatment as fixed effects, patient mean as a random effect and unstructured covariance between regions with each region allowed separate variances were computed for change in medial compartment subregions. Regression models for each region with KLG and Treatment were run for comparison to LME models. Randomization tests (n=200) were run to assess consistency of LME and regression model tests.

RESULTS: Tests for differences between treatment arms and placebo at M6 using regression models for MFTC ΔThCtAB (p=0.014) and LME models for ordered values (p=0.015) were significant, while tests using LME models for subregional change were significant only when interaction terms were included in the model (p=0.02). At M24 only LME models using ordered values were significant (p=0.005); p = 0.995 for MFTC ΔThCtAB and p=0.335 for LME models for subregional change. Randomization tests using LME models had p-values = 0.25 for regional change and p= 0.015 for ordered values at M6, while M24 randomization tests for LME regional models had p-value = 0.48 and ordered values p-value =0.025. The mean difference between randomization test p-value and observed p-value in linear models was 0.003 (SD=0.028) indicating a close correspondence between these two test conditions.

CONCLUSION: Neither mixed effects models or regression models appear to have much test bias for either regional changes or ordered values. Ordered values in mixed effects models were as significant as regional changes at M6 and showed greater significance at M24. A larger number of simulations are needed to improve the precision of results.

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P-26

X-ray acquisition challenges in Clinical Trials: CHALLENGES and solutions POSED BY THE SYNAFLEXER™

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INTRODUCTION: the Synaflexer™ is utilized in many OA trials and by the OAI to standardize positioning. However this device can sometimes cause discomfort for subjects, can be incompatible with many x-ray machines, and may not offer true standardization.

OBJECTIVE: 1) Improve subject comfort when standing on the Synaflexer™ 2) Improve compatibility of the Synaflexer™ with x-ray machines 3) Evaluate the standardization of the Synaflexer ™.

METHODS: In past clinical trial experience in which the Synaflexer™ was used, subject discomfort and x-ray machine incompatibility was reported. The source of the subject discomfort is the chamber that houses the two rows of calibration markers/beads. This chamber protrudes from the back a Synaflexer™ by approximately 5 cm and when a subject of small stature is positioned on the device the chamber comes in contact with the symphysis pubis. Also the Synaflexer is often incompatible with many x-ray machines because the imaging plate/bucky cannot extend to the floor such the standing knee x-ray is not centered on the film and all required anatomy captured on the image. Finally a further challenge uncovered where it was noted that not all Synaflexers™ are identical.

RESULTS: After careful evaluation of two of the challenges a solution was developed and is presented here. A two-part wooden platform was created. Part one is the platform on which the Synaflexer™ is placed. This platform elevates the Synaflexer™ and subject to the average height to which most imaging plates/buckies can extend (See Fig 1). Part two is the wedge which is housed within the platform. This wedge was designed to fit securely around the Synaflexer™ angle and raises the subject such that the likelihood of a subject's symphysis pubis coming in contact with the calibration marker/bead chamber is reduced (See Fig 2, 3 and 4). Also eight Synaflexers™ were evaluated and after careful measurement it was determined that seven of the eight Synaflexers™ were unique in shape as described in Table 1

CONCLUSION: For clinical trials where the Synaflexer™ is used the two-part platform may be necessary to avoid potential subject discomfort and x-ray machine incompatibility. The Synaflexers™ in its current configuration needs further evaluation regarding the effect on image standardization.

#	A	B	C	D
1	11 7/8	11 7/8	3	1 1/4
2	11 3/4	11 5/8	3	1 1/8
3	11 3/4	11 1/2	3	1 1/4
4	11 5/8	11 1/2	3 1/4	1 1/2
5	11 5/8	11 5/8	3	1 1/8
6	11 3/4	11 5/8	3	1 1/8
7	11 3/4	11 5/8	3	1
8	11 3/4	11 5/8	3 1/8	1 1/2

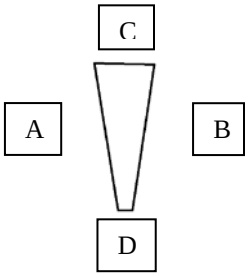

Table 1, and Figure 5. The measurements are of the 4 parts of the trapezium which make up the angled plate for the foot positioning. This means the feet are angled at between 8 and 12 degrees.

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CROSS-SECTIONAL AREA VERSUS VOLUME OF QUADRICEPS MUSCLE AND INTERMUSCULAR FAT IN WOMEN ENROLLED IN THE OAI

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INTRODUCTION: Obesity and muscle weakness are risk factors for both incident and progressive knee OA. We have shown that mid-thigh intermuscular fat (IMF) volume, but not quadriceps muscle (QM) volume, is related to knee strength and physical performance in women with or at risk for knee osteoarthritis (OA). MR images can be analyzed to yield measures of fat and muscle cross-sectional area (CSA) and volume of at a single time point or at serial time points. In evaluating longitudinal changes in tissues, inconsistencies in scanning regions of interest will negatively affect the accuracy of measurements. For this reason, changes in tissue volume are more robust and likely less affected by slight variations in positioning than changes in single slice CSA. However, analyzing a single slice to yield a CSA measurement is much faster and more cost-effective than analyzing many slices to yield a volume. Hence, it is important to understand the extent to which single slice CSA measurements of IMF and QM correlate with volume measurements.

OBJECTIVES: To determine the extent to which 1) MRI-derived volumes of QM and IMF from the right mid-thigh region are adequately represented by a cross-sectional area (CSA) measurement from a single MRI slice and 2) change in QM and IMF volume over 2 years is represented by change in fixed-slice or change in anatomically matched slice CSA.

METHODS: Thirty-five women in the OAI database who were $\geq$50 years old and had baseline and 2 year thigh MRI scans were randomly selected from a sub-cohort of women who i) had baseline and 2-year Kellgren-Lawrence grades available, ii) had adequate thigh MR image registration using baseline and 2-year follow-up scans (shape and $\geq$ 12 matching slices) and iii) had matching pixel spacing. Thigh MRI scans were acquired from a 7.5cm region of interest (15 slices, 5mm slice thickness) beginning 10 cm proximal to the distal femoral epiphysis. Image registration software (Analyze©) was used to match anatomical positioning between baseline and 2-year scans. Software (SliceOmatic©) was then used to segment QM and IMF tissues in the 12 most proximal matching slices resulting in quantification of CSA for each slice and total volume. For cross-sectional associations, slices from only the baseline or the 2 year MRI scan were included for each woman and correlated with total volume. In comparing longitudinal changes, baseline values were subtracted from 2-year measures. Changes in QM and IMF CSA from a given slice and also a matched slice were each compared to changes in total volume of the same tissue. Associations were described using the Pearson's product moment correlations, r, or Spearman's rank order correlations, r_s when data were not normally distributed.

RESULTS: Women included in the analyses ranged in age from 51 to 75 years. Thirteen had symptomatic and radiographic knee OA while 22 had risk factors for knee OA. QM and IMF CSAs in each of the 12 slices were strongly correlated with the corresponding total volumes ($r \geq 0.975$). CSA in slice 10 was strongly and consistently associated with total volume for QM and IMF ($r = 0.998$ and 0.996, respectively). Longitudinal change in CSA in a fixed slice (slice 10 in each of baseline and follow-up images) was associated with change in total volume for QM ($r_s = 0.732$) and IMF ($r = 0.861$). Change in CSA in anatomically matching slices was associated with change in QM volume ($r_s = 0.900$) and IMF volume ($r = 0.879$).

CONCLUSION: For cross-sectional analyses of images acquired at a single time point, it appears that QM and IMF CSAs are highly correlated with total volumes and may be used as a surrogate. However, when assessing changes in tissues over time, it appears that changes in fixed- slice CSA as not as representative of changes in total volume as changes in CSA from matched slices. This observation highlights the importance of performing image registration to match slices anatomically when assessing longitudinal change. Further studies will help to determine if CSA is adequate to assess the relationships between changes in QM and IMF and physical performance or OA progression. Additional analyses will also include the evaluation of smallest detectable differences for QM and IMF CSA and tissue volume.

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THE ASSOCIATION OF MEDIAL TIBIAL AND FEMORAL CARTILAGE MORPHOLOGY TO GAIT BIOMECHANICS IN INDIVIDUALS WITH KNEE OSTEOARTHRITIS

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INTRODUCTION: The peak medial knee joint load during walking predicts radiographic progression of knee osteoarthritis (OA). Cartilage measures from MRI also share relationships with the peak knee adduction moment. However, mechanics that reflect cumulative knee loads, such as loading duration and repetition may also contribute to our understanding of cartilage morphology in knee OA.

OBJECTIVE: The study's purpose was to determine the extent to which the number of steps per day and knee adduction moment (KAM) peak and impulse explain variation in medial tibial and femoral cartilage thickness, volume, and surface area in knee OA.

METHODS: Participants with clinical knee OA (n=33; age 60.7 ± 6.6 years; BMI 28.6 ± 5.8 kg/m^2) were recruited through a rheumatologist. A coronal, 3D SPGRE fat-sat sequence (1.5mm slice thickness) was acquired using a 1T peripheral MRI scanner (GE Healthcare, USA). Medial tibial and femoral cartilage morphometry was segmented using an automated, atlas-based method (Qmetrics, Rochester, USA). Rigid, infrared marker clusters were secured on the sacrum, thigh, shank and foot and tracked using Optotrak position sensors (Certus, Northern Digital, Canada). Ground reaction forces were recorded using embedded force plates (OR6-7, AMTI, USA). Participants performed 5 barefoot walking trials at self-selected speed. The KAM waveform was generated using inverse dynamics software (Visual 3D, C-Motion, USA). The mean number of steps/day was measured over 7 days using a triaxial accelerometer (GT3X, Actigraph, USA). Sequential forward linear regressions were performed for each of medial tibial and femoral cartilage: mean and 5th percentile thickness, volume, and surface area. Two regressions were performed for each dependent variable: BMI and peak KAM (Model 1) or BMI, KAM impulse, and steps/day (Model 2).

RESULTS: Table 1 summarizes the relationships between cartilage morphology outcomes and loading mechanics. In Model 1, 24.8% of variance in 5th percentile of medial femoral cartilage thickness was explained by BMI and the peak KAM ($p<0.05$). No other cartilage measures were related to the peak KAM. By comparison, 23.8% of variance in medial tibial surface area, and 19.4% of medial femoral surface area, were explained by BMI and the KAM impulse ($p<0.05$). No loading variables related to medial cartilage thickness or volume measures in the tibia or femur.

Table 1: Model R^2 values for each dependent measure of medial compartment cartilage morphology.

Cartilage measure	**Medial Tibia**				**Medial Femur**			
	BMI[a]	**PKAM[b]**	**Impulse[c]**	**Steps/day[d]**	**BMI[a]**	**PKAM[b]**	**Impulse[c]**	**Steps/day[d]**
Surface area	0.068	0.177	0.238*	0.290	0.035	0.115	0.194*	0.225
Volume	0.052	0.120	0.164	0.213	0.005	0.036	0.085	0.115
Thickness	0.000	0.001	0.000	0.012	0.025	0.026	0.025	0.046
5th %ile thickness	0.020	0.111	0.100	0.101	0.093	0.248*	0.163	0.169

[a]Step 1 (Models 1&2); [b]Step 2 (Model 1); [c]Step 2 (Model 2); [d]Step 3 (Model 2) *$p<0.05$;

CONCLUSION: Because tibial cartilage morphology related to the magnitude and duration of knee loads in this sample with painful knee OA, measures of medial knee loading show promise in studying cartilage health and degradation. These findings implicate the maximum load experienced at a single time-point, represented by the peak KAM, in focal cartilage defects. Meanwhile, these finding corroborate previous literature suggesting that total loading exposure during a step, represented by the impulse, may play a role in the size of the tibial plateau and femoral condyles.

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P-29

A COMPARISON OF CARTILAGE T2 MAPS GENERATED BY GE, PHILIPS AND SIEMENS

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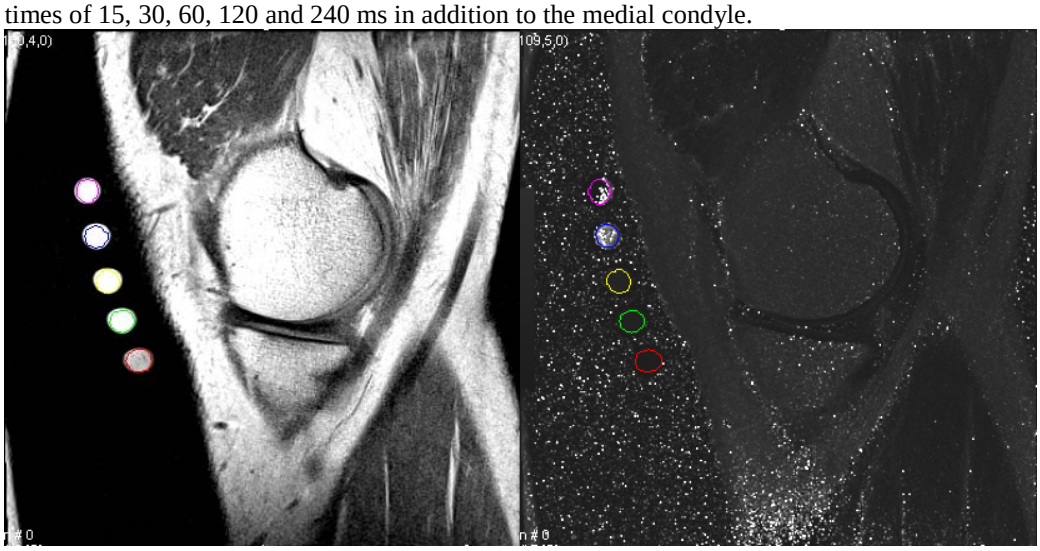
INTRODUCTION: T2 relaxation time in cartilage provides useful measurements as it relates to hydration, macromolecular density and collagen orientation. The three major manufacturers of MRI scanners all provide sequences and software that can be used to generate T2 maps. This study looked at the accuracy and precision of the T2 maps generated by the software on the scanner and compared it to centrally calculated T2 maps.

OBJECTIVE: The goal of this study was to determine the variability that may be associated with T2 relaxation times in a multi-site clinical trial. The first hypothesis is that there is a large variability in the T2 relaxation times calculated by the software on the three different scanners. The second hypothesis is that the T2 relaxation times calculated centrally will be both more accurate and more precise than the T2 relaxation times calculated by the software on the three different scanners.

METHODS: Four volunteer subjects were scanned on three different MR scanners (Siemens Trio 3T, GE Signa HDxt 1.5T and Philips Panorama HFO 1.0T). On each scanner, a T2 mapping sequence was used to scan the medial condyle of the left knee. All subjects were scanned twice on each scanner with repositioning of the patient between scans. Each scan contained five vials with nominal T2 relaxation times of 15, 30, 60, 120 and 240 ms in addition to the medial condyle.



RESULTS: The results show that there is a great deal of agreement between centrally calculated values and values calculated by the three vendors for lower T2 relaxation times (15, 30 and 60ms), and that GE correlates with the centrally calculated values most closely. Philips and Siemens T2 relaxation times tend to differ for longer T2 relaxation times (120ms and 240ms). Full results will be provided at the workshop.

CONCLUSION: When considering utilizing T2 relaxation time in a multi-site, multi-vendor study, variability can be greatly reduced by utilizing centrally calculated T2 maps.

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P-30

PRELIMINARY VALIDATION OF TWO METHODS (HIMRISS, HOAMS) FOR ASSESSMENT OF MRI ABNORMALITIES IN HIP OSTEOARTHRITIS

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INTRODUCTION: Hip OA is an important cause of disability. The prognostic significance of bone marrow lesions (BMLs) on MRI has been suggested in previous histopathological studies. An evaluation of the reliability of hip MRI readings for BML and other joint abnormalities is essential for future longitudinal studies in hip OA. Two previously developed scoring methods were evaluated: 1) the Hip Inflammation MRI Scoring System (HIMRISS), assessing BMLs and effusion/synovitis; 2) the Hip Osteoarthritis MRI Scoring System (HOAMS), a whole joint scoring system.

OBJECTIVE: To evaluate the reliability of MRI readings in hip OA amongst 3 radiologists and 3 rheumatologists using HIMRISS and HOAMS.

METHODS: Methodology was standardized by development of reference training modules, reference images, and calibration after a pilot evaluation of 6 OA patient scans. Six readers (3 radiologists, 3 rheumatologists) participated in 2 reading exercises. In Reading 1, MRIs of the hip of 20 subjects with OA were read for HIMRISS and HOAMS. For HIMRISS, the sum of femoral BML scores (0-65), acetabular BML scores (0-35), effusion score (0-30) and total score was calculated, based on femoral and acetabular subregion readings. In HOAMS, cartilage (0-5), BMLs (0-3), cysts (0-3), osteophytes (0-4), labrum (0-3) and synovitis (0-2) were assessed in femoral and acetabular subregions, as well as effusion (0-2) and other features (0-1). For HOAMS, summed scores for all subregions were also calculated for BML (0-45) and synovitis (0-8). Results from Reading 1 were evaluated and possible sources of discrepancy discussed by teleconference. In Reading 2, MRIs of the hip of 18 subjects from a randomized controlled trial, assessed at two time points, and 27 subjects from a cross-sectional study of hip pain were read for HIMRISS and for HOAMS BML and synovitis scores. Statistical analysis was performed using intra-class correlation coefficient (ICC) for continuous variables. Mean kappa and mean weighted kappa over all reader pairs was calculated for dichotomous and ordinal outcomes, respectively.

RESULTS: Both methods were considered feasible by all readers. For HIMRISS, Reading 1 ICCs were 0.52, 0.61, 0.70 and 0.58 for femoral BML, acetabular BML, effusion and total scores, respectively. For HOAMS, Reading 1 summed BML ICC was 0.52 and summed synovitis ICC was 0.46. For HOAMS, mean weighted kappa ranged from 0.088 to 0.400 for different subregions of cartilage, 0.050 to 0.714 for BML, -0.008 to 0.293 for cysts, 0.267 to 0.397 for femoral osteophytes, 0.008 to 0.148 for acetabular osteophytes, 0.073 to 0.257 for labral lesions, and 0.190 to 0.309 for synovitis. Mean weighted kappa was 0.349 for effusion, 0. 441 for trochanteric bursitis and 0.565 for loose bodies. For Reading 2, HIMRISS ICCs were 0.83, 0.81, 0.66 and 0.84 for femoral BML, acetabular BML, effusion and total scores, respectively, while HOAMS ICCs were 0.85 and 0.62 for summed BML and synovitis scores, respectively. For HOAMS Reading 2, mean weighted kappa ranged from 0.189 to 0.728 for BML subregions and 0.301 to 0.388 for synovitis subregions.

CONCLUSION: There was fair to moderate agreement for individual BML scoring in most subregions. Reliability for summed scores for BML, synovitis and effusion was high and was generally improved with Reading 2 for both HIMRISS and HOAMS. Agreement for other individual joint findings was slight to fair, which may be explained in part by the low prevalence of some joint features. Additional studies are needed to evaluate whether further standardization of readings improves reliability for individual joint features such as cartilage.

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P-31

OCCURRENCE AND SEVERITY OF KNEE OA IN BABOONS: A PRIMATE MODEL FOR HUMAN OA

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INTRODUCTION: Nonhuman primates are critical in OA research because of a paucity of animal models that faithfully mimic the human disease and because of logistic and ethical barriers to studying the earliest stages of OA pathogenesis in humans. Spontaneous (i.e., non-induced) OA is well documented in Old World Monkeys, including the baboon (*Papio hamadryas* spp.), which share with humans many aspects of skeletal anatomy, function, genetics, and disorder. The baboons at the Southwest National Primate Research Center/Texas Biomedical Research Institute (SNPRC/TBRI) are a valuable resource for complex disease studies. They have been studied extensively with regard to bone traits, but until now have not been systematically investigated for OA.

OBJECTIVE: We aimed to characterize knee OA in SNPRC/TBRI baboons and test for age and sex effects. Our hypotheses reflect our belief that the baboon will show trends similar to those found in humans. Our working hypotheses were: 1) Knee OA will be more frequent and severe in older baboons (human equivalent 65+ years). 2) Knee OA severity will be higher in males in younger adult baboons, and higher in females in older adult baboons.

METHODS: We assessed presence and severity of OA in 464 baboons (309 females, 155 males) based on direct visual assessment of the distal femur (Figure 1). These femora were collected at necropsies of SNPRC/TBRI baboons. OA was scored on an ordinal scale from 1 to 4 (Figure 1). Subsequently, we examined reproductive status in females via behavioral records containing data on turgescence (the visible swelling of perineal skin in response to estrogen). We designated each female as pre-menopausal, peri-menopausal, or menopausal and assessed the effect of this covariate. Our sample contains many more aged females than males so we also conducted a second set of analyses on a sample subset (n = 306 [153 of each sex matched for age]). We used a variety of nonparametric tests for significant differences among groups.

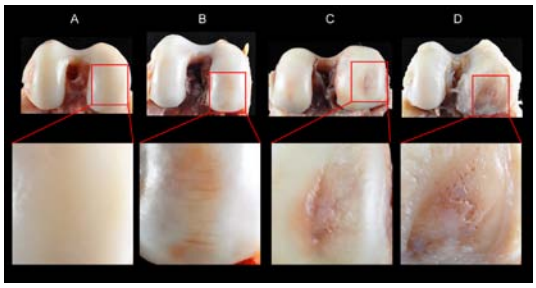

FIGURE 1. Posterior views of distal femora illustrating the four OA classifications: **A**, 1 = Unaffected; **B**, 2 = Mild OA (cartilage fibrillation present); **C**, 3 = Moderate OA (cartilage lesions present); **D**, 4 = Advanced OA (eburnation present). Close-ups of affected areas are shown below each specimen.

RESULTS: As expected, OA was more frequent and severe in older baboons ($p = 0.000001$). The age-matched subset did not show a significant overarching sex effect on OA ($p = 0.069$). However, differential patterns of progression are evident in which males develop knee OA earlier, but females progress more rapidly to advanced disease. With regard to female reproductive status, OA is more severe in peri-menopausal than in pre-menopausal baboons, as in humans ($p = 0.0002$). Menopausal baboons show the highest rates of advanced knee OA.

CONCLUSION: Our results provide important basic knowledge of age and sex trends in knee OA in baboons that support their utility as a model for human OA. We are expanding our investigations in these primates to include radiographic, histological, biochemical, and molecular and statistical genetic analyses focused particularly on early OA, which is so difficult to study in humans.

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ASSOCIATION BETWEEN THE LOWER SERUM HOMOCYSTEIN LEVELS AND THE DOUBTFUL KNEE OSTEOARTHRITIS IN JAPANESE MEN IN EARLY FORTIES

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INTRODUCTION: Homocystein is involved in the metabolic pathway of methionine. High serum homocysteine is a risk factor for a number of chronic illnesses including cardiovascular disease, and osteoporosis. Increase in serum homocystein formed abnormal collagen crosslinks by advanced glycation end products (AGEs), resulting in reduced mechanical properties of tissues, including in bone. As cartilage is also consisted of abundant collagen networks, homocystein and its metabolic products have been suggested to reduce the mechanical properties of cartilage, inducing cartilage damage that is one of risk factors for OA. However, at present, it is reported that there is no association between the serum homocysteine levels and the incident and progression of knee OA. In our university, we are conducting a prospective observational cohort study that is trying to find novel risk factors for metabolic syndrome (MS) in men in early forties.

OBJECTIVE: The aim of this study was to investigate that whether there was an association between serum homocystein levels and the presence of early stage knee OA in men in early forties.

METHODS: One hundred and one men (42 y in aveage), as a volunteer for the MS study mentiond above, were enrolled in this study. In addition to the basal characteristics of the subjects, the blood test and a weight bearing fully extended radiograph of both knee, serum homosystein levels were also measured. The subjects were divided into two groups by the doutful and presence [KLG1 and 2, respectively, (OA group)] and the absence of knee OA (no-OA group). The subjects were categrized by tertiles of serum homocysteine levels. The relation of tertile groups of homocysteine to the presence of radigraphic knee OA was examined. General linear models with the adjustment for age and BMI were used for the comparison. Odds ratios (OR) with 95% CI were calculated to evaluate the prevelence risk for the disease.

RESULTS: Among the subjects, 75 subjects (74.3%) involved in OA group, while remaining 26 (25.7%) in no-OA group. No age, BMI and the prevalence of MS differences were observed between OA and no-OA group, respectively. The subjects in low homocysteine tertile (5.8-8.7 μmol/l) had an increased risk for the prevalence of knee OA over the high homocysteine tertile (10.6-30.9 μmol/l) [OR for high tertile, 5.1 (1.4, 18.4), $p<0.01$]. Serum homocysteine levels of OA group was significantly reduced in comparison to that of no-OA group after adjustment for age and BMI ($p=0.01$). When the subjects were divided into two groups by the serum homocystine value of 8.2 μmol/l (reference lower limit, reference value for men; 8.2-16.9 μmol/l), the subjects whose serum homocystein levels were less than the reference value had an increased risk of prevalence of knee OA in comparison to that of the other subjects [OR 4.9 (1.1, 22.4), $p=0.03$].

CONCLUSION: The past cellular and molecular studies those investigated the homocysteine-related pathophysiology has suggested the possible correlation between serum homocystein levels and the incident and/or progression of knee OA. All these studies were conducted based on the hypothesis that the higher serum homosystein levels could be a risk factor for OA. However, no definite evidence to support this hypothesis has been revealed at present. To elucidate the mechanism of the relationship between the prevalence of knee OA and lower levels of homocysteine, one of the hypothesis is that lower cartilage metabolism could be related to the result of this study. In conclusion, lower serum homocysteine levels, especially for lower than its reference value, were associated with the presence of early stage (doubtful) knee OA in men in early forties.

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NOTES PAGE

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