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	Medial Tibial		P value for difference	Medial femur		P value for difference
	BML	Unaffected by BML		BML	Unaffected by BML	
K^{trans} (1/min)	0.03 (0.02)	0.02 (0.02)	0.018	0.03 (0.03)	0.02 (0.01)	0.188
IAUC	0.14 (0.09)	0.05 (0.03)	0.066	0.13 (0.08)	0.04 (0.02)	0.074
V_e	0.43 (0.39)	0.10 (0.12)	0.274	0.29 (0.25)	0.06 (0.05)	0.080
k_{ep}	12.44 (9.23)	7.13 (7.66)	0.012	10.07 (6.66)	5.68 (5.75)	0.017

area under curve (IAUC), defined as the area under the tissue uptake curve during the first 90 seconds following bolus injection normalized by the area under the AIF over the same period; K^{trans}, the volume transfer constant between blood plasma and extra-cellular extra-vascular space (EES); and k_{ep}, the rate constant between the extracellular space (V_e) and blood plasma which provides an index of the presence of venous hypertension. Statistical comparisons were made within person between regions affected by BML and those that were not affected on both the tibial plateau and femur (for example BML in medial tibia compared to region of medial tibia not affected by BML).

Results: The table depicts the mean (SD) values of perfusion obtained from dynamic contrast enhanced imaging in the different regions of the knee affected and unaffected by BML of six individuals (ranging in age from 48-90 years of age) that were scanned.

Conclusions: Areas of bone affected by BML in knee OA are associated with altered perfusion and intraosseous venous hypertension (k_{ep}) in both the tibial plateau and femur while increased permeability (K^{trans}) was observed in the tibial plateau only. The increase in k_{ep} may be due to the result of obstruction of venous drainage from the affected bone although the causative factor is not yet known. These alterations in bone perfusion and hypertension may be responsible for the bone-remodeling as well as the necrosis of bone occurring in patients with knee OA.

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TWELVE MONTH LONGITUDINAL CHANGE IN REGIONAL CARTILAGE MORPHOLOGY IN A MULTICENTER, MULTIVENDOR MRI STUDY AT 3.0 TESLA - THE A9001140 STUDY

M-P. Hellio Le Graverand[1], B. Wyman[1], R. Buck[1], W. Wirth[2], M. Hudelmaier[3], F. Eckstein[3]
[1]Pfizer Global Research and Development, Ann Arbor, MI; [2]Chondrometrics GmbH, Ainring, Germany; [3]Paracelsus Medical University, Salzburg, Austria

Purpose: Clinical trials for DMOAD evaluation require sensitive methods for detecting significant changes in articular structures over relatively short time periods. Here we investigate whether significant change in regional cartilage morphology can be detected in an enriched OA population (i.e., obese women) in a multicenter, multivendor MRI study at 3Tesla over a period of 12 months.

Methods: 1.0mm coronal FLASHwe MR images of the knee were acquired at baseline and 12 months in 158 female subjects at 7 clinical centers with Siemens and GE scanners. 96 subjects had no symptoms and no evidence of radiographic OA; 62 had medial femorotibial OA on conventional standing AP radiographs (31 Kellgren and Lawrence (KLG) 2 and 31 KLG 3). 7 experienced readers segmented the baseline and follow up images as pairs, with blinding to order of acquisition; all segmentations were quality controlled. The mean cartilage thickness over the entire subchondral bone area (tAB) was computed (ThCtAB). Subregional cartilage thickness was determined for central, anterior, posterior, external and internal subregions of the medial (MT) and lateral tibia (LT), and the weight-bearing medial (cMF) and lateral femur (cLF), using proprietary software (Chondrometrics). The mean change (MC%) and the standardized response mean (SRM = mean/SD of the change) were calculated.

Results: At 12 months, little to no changes were observed in the medial compartment in control subjects (KLG 0), the greatest change being an increase in the ThCtAB in the internal subregion of the MT (SRM=0.20; $p<0.05$). In contrast, in OA subjects, trends to a reduction in the ThCtAB were observed in most cartilage plates in the medial compartment (KLG2 subjects: -0.6%/SRM=-0.19 in MT; KLG 3 subjects: -2.0%/SRM=-0.28 in cMF; $p<0.05$). In the central and external subregions of MT reductions in the ThCtAB attained SRM values of -0.32 and -0.26 in KLG 2 subjects, respectively; in KLG 3 subjects the highest SRM was observed in the external subregion (SRM=-0.22). Increases in ThCtAB were observed in the anterior or posterior subregions of the MT in KLG 3 subjects (SRMs of up to +0.24). In the cMF subregions, reduction in the ThCtAB reached 2.4% in the external (SRM=-0.24) and 4.4% in the central (SRM=-0.40; $p<0.05$) subregions in KLG 3 subjects. In contrast, in the lateral compartment the most significant changes appeared to be increases in ThCtAB. In cLF up to 2% increases in ThCtAB were observed with the most significant changes observed in the internal region in KLG 2 subjects (SRM=+0.38; $p<0.05$) and in the external and central regions (SRM=+0.38; $p<0.05$ and +0.32 respectively) in KLG 3 subjects. In cLT, at the total plate level no changes were observed likely related to a cancelling effect of both increases and decreases in certain subregions. In KLG 2 subjects, increases up to 2% in the external and posterior regions were observed (SRM=+0.40; $p<0.05$ and +0.35 respectively) and in KLG 3 subjects increases up to 2.8% were observed in the anterior region (SRM=+0.40; $p<0.05$).

Conclusions: Little to no changes in cartilage thickness were observed in control subjects at 1 year. Relatively small changes in cartilage thickness were observed at total plate level in KLG 2 and 3 subjects over 1 year, mostly including reductions in the medial compartment and increases in the lateral compartment. Subregional analysis revealed greater sensitivity to change in cartilage thickness in some subregions, including reductions in the external and central subregions of MT and cMF.

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DIAGNOSTIC PERFORMANCE OF IN VIVO MRI FOR ARTICULAR CARTILAGE ABNORMALITIES IN HUMAN OSTEOARTHRITIC KNEES USING HISTOLOGY WITH SAFRANIN-O STAINING AS STANDARD OF REFERENCE

E. Saadat[1], B. Jobke[2], J. Cheng[2], X. Li[2], R.I. Bolbos[2], M.D. Ries[3], S. Majumdar[2], T.M. Link[2]
[1]UCSF School of Medicine and UCSF Department of Radiology, San Francisco, CA; [2]UCSF Department of Radiology, San Francisco, CA; [3]UCSF Department of Orthopaedic Surgery, San Francisco, CA

Purpose: To evaluate the sensitivity and specificity of in vivo 3T Magnetic Resonance Imaging (MRI) in the assessment of cartilage pathologies of the knee, by using histology as the reference standard in patients undergoing total joint replacement.

Methods: Eight knees of seven patients (3 males and 4 females, average age 65.6 years) with advanced osteoarthritis of the knee and scheduled for total joint replacement were examined with 3T

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Score	Thickness		Surface		Signal pattern	
	MRI	Histology	MRI	Histology	MRI	Safranin-O staining intensity
0	Normal	Normal	Normal	Normal	Homogeneous	Normal/slight reduction
1	<50% loss	Mild reduction	Fraying	Slight fibrillation	Inhomogeneous	Moderate/severe reduction
2	>50% loss	Severe reduction	Fibrillation	Severe fibrillation		
3	Complete loss	Complete loss				
4	Swelling	Swelling				

MRI using a quadrature knee coil and a clinical fat saturated intermediate weighted fast spin echo (iw FSE) sequence (TR/TE = 9.3/3.7 msec). Tibial plateaus and femoral condyles of the knees were resected during surgery, marked to allow comparison with MRI and fixed in 10% formalin. Sagittal histologic sections (4 μm thick) from each cartilage piece were obtained in the same orientation as the MR scans and stained with Safranin-O, Hematoxylin and Eosin for histological analysis. Less-severely affected compartments of the knee were used for this study.
Intraoperative information, edge-distance measurements and morphological features were used to match corresponding MRI and histology sections by four investigators (BJ, TML, ES and JC) in consensus. Three to six 0.5-1 cm wide (sagittal diameter) "observation units" (OUs) were defined for each of the obtained cartilage samples for comparison of the MRI findings to histological features. The MRI findings of each OU were compared to the corresponding region in the histological section for thickness and surface integrity using the grading system outlined in Table 1.
The MRI signal pattern was compared to the proteoglycan content of the corresponding OU in histology as determined semiquantitaively by Safranin-O staining. The histological sections were scored by a trained musculoskeletal pathologist (BJ) in parallel to the clinical MRI readings by a musculoskeletal radiologist (TML). Statistical methods used included calculation of sensitivity and specificity.
Results: The overall sensitivity and specificity for the thickness, surface and signal pattern readings are reported in Table 2.

Table 2

	Thickness	Surface	Signal pattern
Sensitivity	72% (*75%*)	57% (*72%*)	37% (*37%*)
Specificity	66% (*69%*)	68% (*72%*)	52% (*52%*)

The iw FSE images correctly revealed pathologic thinning of cartilage with 72% sensitivity, but specificity was lower (66%). The outcome was reversed with regards to the cartilage surface abnormalities: The iw FSE images were not sensitive to cartilage surface abnormalities such as fraying and clefts (57% sensitivity), but MR diagnosis of normal cartilage corresponded to histopathologically normal cartilage more frequently (68% specificity). The sensitivity and specificity for all measures increased when the data was dichotomized (normal vs. diseased cartilage with no grading of disease severity-Table 2, bold numbers). Cartilage MR signal changes did not correlate with degeneration as graded semiquantitaively by Safranin-O staining.
Conclusions: Our results indicate that cartilage pathology with loss of cartilage thickness is relatively well predicted using iw FSE sequences, however sensitivity for cartilage surface integrity is lower. The iw FSE signal pattern, on the other hand is not sensitive or specific for the proteoglycan content of the tissue as diagnosed semiquantitaively by Safranin-O staining, indicating the need for other MR techniques in this regard.

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BONE MINERAL DENSITY ASSESSED BY COMPUTED TOMOGRAPHY IN AN IN VIVO RABBIT MODEL OF OSTEOARTHRITIS

M. Bouchgua, K. Alexander, E. Carmel, G. Beauchamp, H. Richard, S. Laverty, **M. Bouchgua**
University of Montreal, Montreal, PQ, Canada

Purpose: To assess, using clinical computed tomography (CT) equipment, changes in bone mineral density (BMD) at different depths from the articular surface in an in vivo rabbit model of osteoarthritis (OA).
Methods: Unilateral transection of the anterior cruciate ligament (ACLT) was performed on a randomly assigned femorotibial joint in skeletally mature male New Zealand White rabbits (n=10). A sham surgery was performed on the contralateral joints (n=10). Control rabbits (n=6) did not undergo surgery. Knee joints, stabilized within a plexiglass mould, were placed longitudinally on a solid dipotassium phosphate bone density calibration phantom (13002 Model 3 CT Calibration Phantom, Mindsways Software, Inc, San Francisco, California, United States) and scanned in a transverse image plane with a helical single-slice CT scanner (Hi-Speed ZXi, General Electric, Mississauga, Ontario, Canada). Density data in Hounsfield Units was obtained from oval regions of interest (ROI), placed in each phantom rod and each epiphyseal compartment (lateral femoral condyle LFC, medial femoral condyle MFC, lateral tibial plateau LTP, medial tibial plateau MTP). BMD was calculated using linear regression. BMD was calculated at depths of 1, 2, 3, 4, 5 and 6 mm from the articular surface in the femur and at 1, 2 and 3 mm in the tibia (to the growth plate). Baseline BMD measurements were made at 2 weeks before surgery (week -2), and then repeated at weeks 2, 4 and 8 post-surgery for all 10 ACLT rabbits, and at week 12 for 5 of the ACLT rabbits. BMD was measured at weeks -2 and 8 in the 6 control rabbits to detect any changes related to time in normal animals. The evolution of BMD over time and the differences between depths, and compartments were assessed within and between groups using a repeated-measures linear model with depth and time as within-subject factors.
Results: For the control group, BMD decreased with increasing distance from the articular surface. The majority of BMD calculations at all depths in all compartments remained stable over time. In the ACLT and sham groups, of the significant changes occurring, 81% were detected in the ACLT joints and the majority were highly significant ($p<0.001$). A reduction of BMD over time was the most frequent change observed in the ACLT joints. This significant reduction was observed by week 2 post-operatively in 3 (LFC, MFC and MTP) out of 4 compartments in the ACLT joints, but not in the sham joints. At week 12 the significant reduction in BMD persisted in all 4 compartments but not at all depths of the ACLT joints. In the MFC of ACLT joints, at weeks 4, 8 and 12 the reduction in BMD was observed to occur at greater depths into the bone (reduction measured at all 6 depths at week 8). By comparison these changes were restricted to depths of 1 and 2 mm in the LFC. At week 8 in the LTP and MTP, reductions were measured at all 3 depths in the ACLT group, but overall they occurred more frequently in the MTP. At week 12, a