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Abstract 310 – Table 1

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 semi-quantitaively 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

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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

modest reduction was observed in the LTP (p=0.047) and MTP (p<0.024) of the sham joints.
Conclusions: Clinical CT equipment permitted easy and non-invasive assessment of the BMD temporally (ACLT and sham) in an in vivo OA rabbit model.

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AUTOMATIC KNEE CARTILAGE VOLUME QUANTIFICATION COMPARED TO JOINT SPACE WIDTH: BIOMARKERS OF LONGITUDINAL PROGRESSION?

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Purpose: For clinical studies, diagnostic and prognostic biomarkers are needed to select a population at the target stage of osteoarthritis (OA) with a high risk of progression; and an efficacy biomarker is needed to quantify the treatment effect. Currently, diagnostic and prognostic markers are available, but the development of progression biomarkers has proved to be challenging. The aim of this study was to evaluate whether a fully automatic cartilage volume quantification method is suitable as a biomarker for quantification of longitudinal progression of knee OA. For perspective, the results are compared to joint space width (JSW) quantification.
Methods: A study population was prospectively selected with 159 subjects with age 21 to 81 years (mean 56), BMI 19 to 38 (mean 26), and 48% female. Radiographs were acquired in a load-bearing semi-flexed position using the SynaFlex. MRI scans with near-isotropic voxels were acquired from a Turbo 3D T1 sequence on a 0.18T Esaote scanner (40° FA, TR 50 ms, TE 16 ms, scan time 10 min, resolution 0.7 x 0.7 x 0.8 mm^3). Radiographs and MRI were acquired for both left and right knees at baseline (BL), after one week for a subgroup of 31 knees, and at follow-up (FU) after 21 months. After exclusion of 25 knees used for training of the computer-based method, 288 knees were in the study at BL and 245 knees at FU.
Kellgren and Lawrence (KL) score and JSW were evaluated from the radiographs in the medial tibio-femoral compartment and tibial and femoral cartilage volume was quantified in the medial compartments by a fully automatic framework. JSW and volume were normalized by the tibial plateau width.
At BL, the distribution of KL scores was (145,88,30,24,1) for KL 0-4. At FU, 25 knees had progressed from healthy to OA (KL>0) and 101 had remained healthy.
Results: At BL, the mean total cartilage volume was 6851 mm3 with a scan-rescan CV of 3.6% (since the method is fully automatic, the intra-scan CV was zero). The volume quantification allowed diagnostic separation at BL of healthy from OA (p<0.001) as well as from early OA (KL 1, p<0.01), see Figure 1. The BL volume predicted progression with borderline significance (p=0.08). Finally, the measured cartilage loss was higher for progressors than non-progressors (p<0.01), see Figure 2 (right). For comparison, JSW provided diagnostic separation of healthy from OA (p<0.001) and from early OA (p<0.01) - but allowed neither prognostic (p=0.3) nor progression separation (p=0.4, Figure 2 left).
Conclusions: Since JSW is an integral part of the KL score, the diagnostic ability was expected. However, the results indicated that the use of JSW as outcome measure in longitudinal studies is questionable. Cartilage volume was suitable as diagnostic marker and borderline suitable as prognostic. More importantly, the volume quantification showed increased cartilage loss for the OA progressors compared to the non-progressors (p<0.01). Thereby, the fully automatic computer-based method may be suitable for use as a treatment efficacy marker in longitudinal studies.

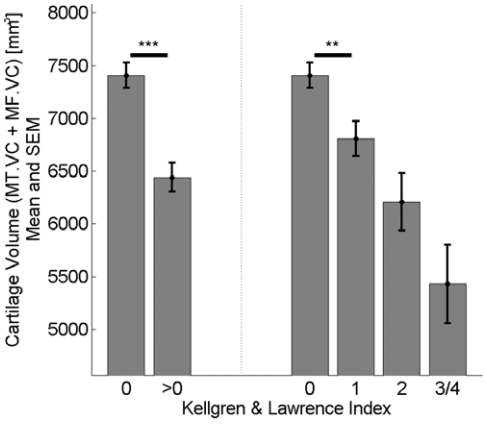

Figure 1. Left: Volume allowed separation of healthy (KL 0) from OA (KL>0). Right: There was a clear linear trend of reduced cartilage volume with increasing KL score.

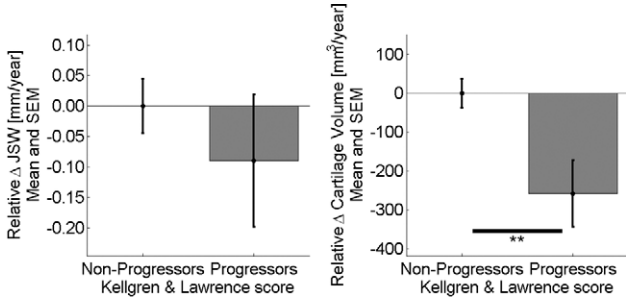

Figure 2: Left: The JSW change failed to separate progressors from non-progressors. Right: The cartilage volume loss was higher for the progressors (p<0.01).

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T2-STAR RELAXATION AS A MEANS TO DIFFERENTIATE CARTILAGE REPAIR TISSUE

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Purpose: The capability of magnetic resonance imaging (MRI) to visualize morphological and biochemical changes of articular cartilage give it the potential to follow-up different therapy procedures. A possible non-invasive statement about the produced cartilage repair tissue remains challenging and founded the need for modern evaluation techniques such as quantitative T2 mapping. However its clinical use with sufficient signal to noise and high resolution is limited by relatively long scan time. Underlying reliable results, T2 star mapping with its possible short scan time seems to offer a potential alternative. In a recent study of our group the accuracy and efficiency of the used T2 Star fitting algorithm was validated and the use of T2 star maps, created in clinically acceptable time frames and with resolutions that allow a detailed analysis of the cartilage, was shown.
The goal of the presented feasibility study was to use T2 star mapping in the follow-up of two different cartilage repair procedures and to compare it to the established T2 mapping by a multi-echo spin-echo (SE) technique.
Methods: One group of 15 healthy volunteers and two patient