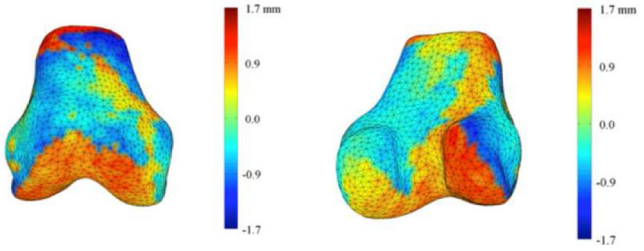
mechanics, particularly mechanical stress in the cartilage, is largely responsible for disease pathology. Since stress in the cartilage is highly dependent upon the geometry of the joint, among other biomechanical and physiological factors, it is not surprising that imaging biomarkers based on high fidelity bone shape descriptors are significantly different in individuals who are at risk of developing radiographic knee OA (RKOA) and those who are not, and that baseline subchondral bone shape is a significant predictor of the onset of RKOA 12-months prior to onset. We tested the hypothesis that high fidelity descriptors of distal femur subchondral bone shape are significant predictors of future RKOA and that these shape descriptors are different in males compared to females.

Methods: The Osteoarthritis Initiative (OAI) is a multi-center, longitudinal, observational cohort study focused on identifying biomarkers for the development or progression of knee OA. From an ongoing case-control longitudinal OAI study, we identified a group of subjects within the OAI Incidence subcohort that presented with no signs of knee OA per the OAI definition (KL=0 in both knees) at baseline and at the 36- or 48-month visit (control group; n=32). We also identified age- and sex-matched subjects from the OAI Incidence subcohort who presented with no signs of knee OA at baseline (KL=0 in both knees) who then went on to develop knee OA (KL>=2 in any knee) by the 36- or 48 month visit (case group; n=32). Baseline axial MRI image data sets were processed to extract the distal femur bone surface and a statistical shape model (SSM)of the distal femur representing the entire cohort (n=64). We tested for differences in mean SSM shape mode weighting factors (WFs) between the case and control groups, and between males and females (JMP Pro, v.10, SAS Institute, Cary, NC). Using stepwise logistic regression (JMP Pro, v.10, SAS Institute, Cary, NC) we tested the ability of baseline SSM WFs to predict the future onset of RKOA at least three years post baseline imaging for the whole cohort and for males and females separately. Sensitivity and specificity of the resulting predictions of future RKOA were quantified using the area under the receiver operating characteristic curve (ROC AUC).

Results: A total of six distal femur SSM WFs were significantly different between case and control knees for males. Three SSM WFs were significantly different between case and control knees for females. Using stepwise logistic regression with case or control status as the outcome variable, three SSM WFs were selected for males and six WFs were selected for females. The resulting area under the ROC curve for the logistic model using the three selected SSM WFs for males was 1.0 and the AUC for the model constructed form the six SSM WFs for females was 0.975.

Conclusions: Subchondral knee bone shape differs significantly between knees that later developed RKOA and those that did not. This difference is detectable at least three years prior to the onset of RKOA. Predictions of the future onset of RKOA can be made with high specificity and sensitivity using independent, high fidelity, shape descriptors of the distal femur. In addition the high fidelity SSM parameters describing these differences are not the same for men compared to women. Distal femur subchondral bone shape variability associated with future onset of RKOA appears to be more complex in females compared to males since the number of shape variables (6) used to construct an accurate predictive model for females was larger than the number of shape models required to construct an accurate predictive model for males (3). While, on average, the incident knees generally had higher condylar curvature and greater varus orientation, knee shape differences between cases and controls are much more complex and cannot be easily described using gross discrete measures (Fig. 1). These results warrant further investigation to determine how the identified subchondral bone shape variations affect knee mechanics, particularly the stresses encountered within the knee cartilage and subchondral bone.



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A MAGNETIC RESONANCE IMAGING BASED RAPID KNEE CARTILAGE QUANTIFICATION METHOD FOR THE LATERAL TIBIOFEMORAL COMPARTMENT: DATA FROM THE OSTEOARTHRITIS INITIATIVE

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Purpose: Cartilage morphometry on magnetic resonance images (MRIs) is becoming an acceptable outcome measure for clinical trials among individuals with knee osteoarthritis (OA). However, obtaining accurate and reproducible cartilage data is burdensome. In previous work, we designed and validated a rapid knee cartilage quantification method_-cartilage damage index (CDI) – for the medial tibiofemoral compartment. The purpose of this study was to expand and validate the CDI to detect cartilage damage in the lateral tibiofemoral compartment.

Methods: This was an iterative process where we developed the measure, conducted preliminary tests of validity, and then tested its construct validity. For this process, we created 3 datasets: development (100 knees), testing (83 knees), and validation (100 knees). (1) Development: For the development dataset, we chose 100 knees from the Osteoarthritis Initiative (OAI) baseline that included knees with all grades of lateral joint space narrowing (JSN, grades 0-3) with and without medial JSN. The MRIs are 3-dimensional double-echo steady-state sagittal images that were obtained on four 3-Tesla systems (0.37 mm x 0.37 mm, 0.7 mm slice thickness). To develop the lateral tibiofemoral CDI we identified areas commonly affected by denudation by having one reader manually mark the lateral cartilage denudation on each knee. We then designed a pair of two dimensional, rectangular, universal coordinate systems to represent the articular surface of the distal lateral femur and proximal lateral tibia. Next, we projected the denudation regions onto a coordinate system and selected 18 informative locations in and around the region that most frequently contained denudation (Figure 1). The primary outcome is a CDI, which summates the products of cartilage thickness, cartilage length and voxel size from each informative location and are adjusted by height. (2) Testing: On 83 knees with publicly available MRI-based cartilage segmentation (Imorphics LTD) we did preliminary tests to explore face and construct validity. One reader used customized software to measure the CDI in the lateral femur and tibia cartilage in the testing and validation datasets. (3) Validation: We selected 100 knees with baseline and 24-month MRIs that was enriched to include all levels of lateral JSN and individuals with and without lateral JSN progression. 20 knees were selected from this final validation dataset to assess intra-tester

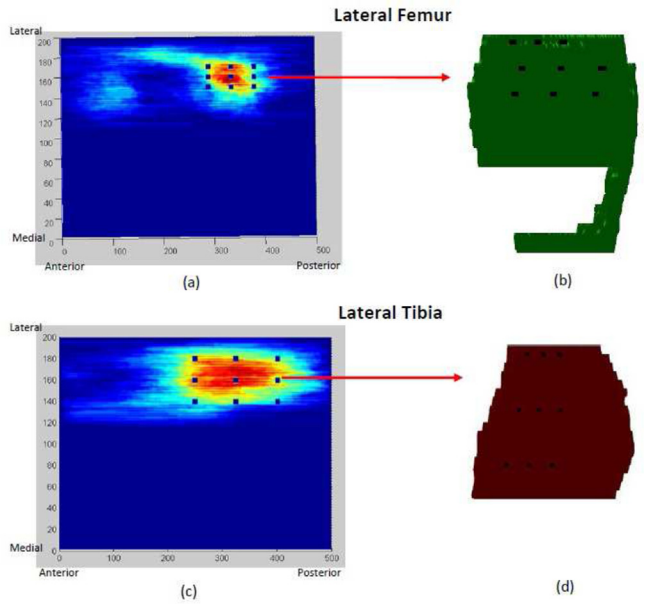

Figure 1(a), (c) Lateral Femur and Tibia denuded projection and 18 informative locations on the coordinate system, (b), (d) Corresponding denuded peak on the cartilage map. Note: cartilage maps were rotated to better display informative locations.

reliability. We validated the lateral CDI by examining the association between baseline (month 0) lateral CDI, lateral joint space narrowing (OARSI score 0-1), lateral joint space width (JSW), and static alignment (hip-knee-ankle [HKA] angle). We calculated standard response mean (SRM) for lateral CDI change between baseline and 24-months. JSW data and descriptions of the methods are publicly available on the OAI website (kxr_qjsw_duryea_00 [version 0.5] and kxr_qjsw_duryea_03 [version 3.4]; http://oai.epi-ucsf.org/). HKA was measured on standing full-limb radiographs (developed by Derek Cooke, ICC>0.99).

Results: The final validation set included 100 knees with a mean age: 64.3 years, 59% females, and with a diverse range of lateral JSN grades (0 to 3, each grade contains 25 subjects) as our final validation dataset. The intra-tester reliability is good (intraclass correlation coefficient ICC [3, 1 model] = 0.86 to 0.98). At baseline, knees with greater medial JSN and KL had lower mean CDI (i.e. greater cartilage damage, Table 1). Baseline lateral CDI is associated with both lateral JSW and HKA (see table 2).The SRM is good (SRM=-0.76 for lateral femur; SRM=-0.73 for lateral tibia; SRM=-0.87 for lateral tibiofemoral total).

Table 1
Baseline lateral cartilage damage index stratified by baseline lateral JSN and KL grade.

			Lateral JSN			
Cartilage Measure	JSN=0 (n=25) mean	JSN=1 (n=25) mean	JSN=2 (n=25) mean	JSN=2 (n=25) mean	p-value for trend	
Lateral Femur CDI	2969.3	3003.2	2184.4	1542.0	<0.001	
Lateral Tibia CDI	1154.9	889.9	663.8	392.7	<0.001	
Lateral Tibiofemoral CDI	4124.3	3893.0	2848.2	1934.6	<0.001	
			KL			
	KL=0 (n=10) mean	KL=1 (n=6) mean	KL=2 (n=32) mean	KL=3 (n=26) mean	KL=4 (n=26) mean	p-value for trend
Lateral Femur CDI	2718.7	2831.5	3061.0	2254.0	1605.3	<0.001
Lateral Tibia CDI	1229.3	994.1	946.3	690.4	424.7	<0.001
Lateral Tibiofemoral CDI	3948.0	3825.5	4007.3	2944.4	2030.0	<0.001

Table 2
Spearman correlation of baseline lateral CDI with baseline lateral JSW and HKA angle.

Cartilage Measure	Lateral JSW	HKA
Lateral Femur CDI	0.81*	-0.31*
Lateral Tibia CDI	0.81*	-0.30*
Lateral Tibiofemoral CDI	0.85*	-0.33*

Note: * = p<0.05.

Conclusions: Overall, the lateral tibiofemoral CDI quantification is reliable, responsive, and has good construct valid. The CDI has utility for deployment in large studies.

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CHANGE IN CARTILAGE T2 RELAXATION TIME IN OSTEOARTHRITIC KNEES WITH AND WITHOUT STRUCTURAL PROGRESSION – PILOT DATA FROM THE OSTEOARTHRITIS INITIATIVE

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Purpose: MRI-based measurement of spin-spin (transverse) relaxation time (T2) of articular cartilage is of interest because of its potential sensitivity to changes in cartilage composition. However, it is unknown whether cartilage T2 predicts structural progression (i.e. cartilage loss in MRI and radiographic joint space width [JSW] loss) in knee osteoarthritis (OA), and to what extent T2 changes longitudinally in knees that exhibit structural progression. The objective of the current study was therefore to compare baseline cartilage T2 and longitudinal change in T2 between knees with and without structural progression in the medial femorotibial compartment.

Methods: OA knees with and without structural progression in the medial femorotibial compartment (MFTC) were selected from a subcohort of the OAI (n=625), for which baseline and 1-year follow-up measurements of MRI-based cartilage thickness and radiographic JSW were available. 45 knees with Kellgren & Lawrence grade 2/3 showed structural progression in the MFTC that exceeded the smallest detectable change (SDC) thresholds for both MRI-based cartilage thickness (102μm) and radiographic JSW (328μm) over the same period. Of these, 37 could be matched to one of the 202 knees from the same subcohort without any progression in the MFTC or the lateral compartment (LFTC). Knees were matched 1:1 by KLG, BMI, sex, and knee pain status.

Thus far, cartilage T2 analyses were completed in 22 of the 37 matched case-control pairs (17 women/5 men; 13KLG 2/9 KLG3; cases: age: 63.8±9.0 y, BMI: 30.6±5.0 kg/m^2; controls: 65.5±10.6 y, 30.8±4.4 kg/m^2). A multi-echo spin-echo MRI sequence was used (resolution: 0.31x0.31x3mm, repetition time: 2700ms, echo time: 10, 20, 30, 40, 50, 60, 70ms, 1st echo excluded from analysis) and manual segmentation of the medial and lateral tibial (MT/LT) and medial and lateral weight-bearing femoral condyles (cMF/cLF) was performed with blinding to the progressor/non-progressor status and the image acquisition order. T2 was computed in the deep and superficial layer of each cartilage plate (each 50% of the thickness) using a non-linear curve-fitting. Paired t-tests were used to compare baseline and follow-up measurements within progressors and non-progressors, and to compare both groups cross-sectionally (at baseline) and longitudinally.

Results: The baseline T2 did not differ significantly between OA knees with and without subsequent medial progression (p≥0.09, Table). Despite the substantial cartilage thickness loss in the MFTC of the progressors (Mean±SD: -280 ±160μm, p<0.001), no significant change in T2 was observed in MFTC (p≥0.10, Table). The T2 tended to increase

Baseline T2 (ms) and change in T2 in the cartilages of progressors (P) and non-progressors (NP)

		Baseline					Change						
		P		NP		P vs.NP	P			NP			P vs. NP
		Mean	SD	Mean	SD	P-Value	Mean	SD	P-Value (change)	Mean	SD	P-Value (change)	P-Value
MT	Deep Layer	35.8	3.1	35.6	3.5	0.89	1.4	3.9	0.10	-0.7	1.5	0.05	0.05
	Superficial Layer	44.8	3.0	43.6	2.9	0.12	-0.6	2.9	0.31	-0.1	2.1	0.83	0.42
cMF	Deep Layer	45.5	5.0	46.4	8.1	0.66	1.9	5.4	0.11	-0.1	4.3	0.90	0.06
	Superficial Layer	54.0	4.3	51.6	4.7	0.09	0.4	5.7	0.72	0.3	3.0	0.70	0.89
LT	Deep Layer	32.9	2.1	32.5	2.5	0.53	0.1	1.5	0.82	-0.1	1.3	0.60	0.61
	Superficial Layer	43.0	2.9	43.3	3.1	0.74	-0.1	1.6	0.86	-0.7	1.6	0.06	0.24
cLF	Deep Layer	41.9	3.7	41.7	2.5	0.80	-0.3	2.2	0.50	-0.5	1.7	0.20	0.74
	Superficial Layer	50.3	4.5	49.4	4.4	0.54	-1.1	2.1	0.03	-0.7	2.2	0.17	0.55