Time-saving opportunities in knee osteoarthritis: structural imaging and T_2 mapping in the knee using a single 5-minute MRI scan

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ABSTRACT

Objective: To assess the discriminative power of a 5-minute quantitative double-echo steady-state (qDESS) sequence for simultaneous T_2 measurements of cartilage and meniscus, and structural knee osteoarthritis (OA) assessment, in a clinical OA population, using radiographic knee OA as reference standard.

Methods: 53 subjects were included, divided over three groups based on radiographic and clinical knee OA: 20 subjects with no OA (Kellgren-Lawrence Grade (KLG) 0), 18 with mild OA (KLG2) and 15 with moderate OA (KLG3). All patients underwent a 5-minute qDESS scan. We measured T_2 relaxation times in four cartilage and four meniscus regions-of-interest (ROIs) and performed structural OA evaluation with the MRI Osteoarthritis Knee Score (MOAKS) using qDESS with multiplanar reformatting. Between-group differences in T_2 values and MOAKS were calculated using ANOVA. Correlations of the reference standard (i.e., radiographic knee OA) with T_2 and MOAKS were assessed with correlation analyses for ordinal variables.

Results: In cartilage, mean T_2 values were 36.1 ± SD 4.3, 40.6 ± 5.9 and 47.1 ± 4.3 ms for no, mild, and moderate OA, respectively ($P<0.001$). In menisci, mean T_2 values were 15 ± 3.6, 17.5 ± 3.8 and 20.6 ± 4.7 ms for no, mild, and moderate OA, respectively ($P<0.001$). Statistically significant correlations were found between radiographic OA and T_2 and between radiographic OA and MOAKS in all ROIs ($P<0.05$).

Conclusion: Quantitative T_2 and structural assessment of cartilage and meniscus, using a single 5-minute qDESS scan, can distinguish between different grades of radiographic OA, demonstrating the potential of qDESS as an efficient tool for OA imaging.

INTRODUCTION

The growing population suffering from knee osteoarthritis (OA) and the lack of early biomarkers and therapeutics prompt the need for efficient imaging methods [1]. Magnetic resonance imaging (MRI) allows assessment of the whole knee joint, making it ideally suited for imaging in knee OA, which is a multi-tissue disease [2,3]. Several potential MRI-based biomarkers have been proposed in this context [4]. In particular, the role of quantitative MRI (qMRI) techniques is emerging. qMRI techniques, such as T_2 mapping, have the ability to non-invasively detect subtle changes in biochemical composition of tissues such as cartilage and menisci. Increased T_2 relaxation times have been shown to be associated with cartilage and meniscus degeneration, potentially enabling early stage detection of knee OA and similar conditions [5-8]. T_2 mapping does not require a contrast injection or special MRI imaging hardware and numerous techniques for post-processing of T_2 images are available [5,7,9,10].

Besides quantitative MR imaging, structural evaluation of the knee is fundamental in the assessment of knee OA, given its multi-tissue nature [2,3]. The semi-quantitative MRI Osteoarthritis Knee Score (MOAKS) [11] is a widely used and well-validated instrument for evaluating knee OA, and has been applied in large scale epidemiological OA studies such as the Osteoarthritis Initiative (OAI) [11-14].

T_2 mapping and MOAKS are potential biomarkers to non-invasively assess joint health; however, acquiring them efficiently is a challenge. In general, multiple sequences are used in knee OA imaging, often resulting in time consuming MRI protocols that take 30-45 minutes or longer [6,15]. In particular, in the context of large-scale clinical trials and repeated measurements, MRI acquisition can create a significant burden for patients, hospitals, and research budgets. In the context of quantitative MRI, multiple sequences also bring up the need for registration between sequences. Hence, creating more streamlined MRI protocols and reducing acquisition time is of great interest.

In the present study, we evaluated a novel MRI technique to reduce scan time in the context of knee OA: the quantitative double-echo steady-state (qDESS) sequence. qDESS generates two echoes: one echo with T_1/T_2 weighting (resembling proton-density contrast), and one echo with T_2 weighting. It has the potential to provide diagnostic images as well as quantitative measurements (i.e., T_2 maps) of the knee in a single sequence with an acquisition time less than five minutes [16,17].

Proof-of-concept of qDESS for T_2 mapping of cartilage and meniscus and structural knee assessment (using MOAKS) has been provided by Chaudhari et al. [16]. Focusing on healthy subjects, they validated qDESS against routine methods for T_2 measurements and MOAKS and reported high accuracy in most tissues. Also, a pilot study in 10 patients with knee OA, performed in the same work, provided promising qDESS-based T_2 mapping and MOAKS outcomes, suggesting that accurate knee OA measurements are possible with qDESS [16]. Building upon this work, we further assessed the discriminative power of quantitative and structural qDESS-based biomarkers, in a larger OA cohort against radiography, widely accepted as the gold standard for knee OA imaging [18,19]. We evaluated structural MOAKS scores and T_2 measurements of the knee cartilage and meniscus in a clinical OA population. In contrast to the approach of Chaudhari and colleagues, which comprised a global assessment of cartilage and menisci, in the present study we evaluated predefined subregions of cartilage and menisci. Regional assessment is relevant as knee OA is a focal disease with an heterogenous disease pattern [6,20,21].

The aim of the present study was to assess the discriminative power of a single 5-minute qDESS MRI sequence for simultaneous T_2 measurements of cartilage and meniscus, and structural knee OA assessment, in a clinical osteoarthritis population, using radiographic knee OA as a reference standard.

METHODS

Study population

This study was performed with approval from our Institutional Review Board and in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations. Written informed consent was obtained from all participants after receiving full explanation about the study. Consecutive patients who were referred by the Department of Orthopedic Surgery for knee MRI at Stanford Medical Center between December 2016 and July 2017 were screened for eligibility. The eligibility criteria for this study are shown in Table 1. Based on radiographic (Kellgren and Lawrence grade (KLG) [22]) and clinical (American College of Rheumatology (ACR) criteria [23]) degree of knee OA, three subject groups were selected: subjects with no

Table 1. Eligibility criteria

Non-OA subjects	**OA-subjects**
Referred for knee MRI	Referred for knee MRI
No contra-indication for MRI	No contra-indication for MRI
AP weightbearing radiograph of index knee[a] available	AP weightbearing radiograph of index knee[a] available
No ACL reconstruction in index knee in medical history	No ACL reconstruction in index knee in medical history
KLG0	KLG2 or KLG3
	Knee pain + at least 1 of 3: 1, Age > 50 years 2. Stiffness < 30 minutes 3. Crepitus

a Acquired within 2 weeks before or after MRI acquisition
Abbreviations: OA = osteoarthritis, MRI = magnetic resonance imaging, AP = anteroposterior, ACL = anterior cruciate ligament, KLG = Kellgren Lawrence grade

OA (KLG0 and ACR negative), subjects with mild OA (KLG2 and ACR positive), and subjects with moderate OA (KLG3 and ACR positive).

Scoring of radiographic knee OA

The assessment of radiographic knee OA was performed according to the KLG criteria [22], by a researcher with a medical degree and four years of experience in musculoskeletal imaging research (SE) who was blinded to any patient data. Standardized, weight-bearing AP radiographs were used. A second reader, a musculoskeletal radiologist with 15 years of experience (EO) also performed the KL grading in a random selection of 20 subjects from the study population to assess interobserver reliability. To assess intra-observer reliability of the primary observer (SE) 20 randomly selected subjects from the study population were re-evaluated 14 days after initial grading.

MR imaging data acquisition

MR imaging was performed on one of two identical 3-Tesla MR scanners (Discovery MR750, GE Healthcare), using a 5-minute 3D sagittal qDESS scan with an 8-channel transmit-receive knee coil (InVivo). qDESS generates two echoes per repetition time: S+ (with T_1/T_2 contrast; echo time (TE) 5.7 ms; Figure 1a), and S- (with T_2 weighting; TE 30.1 ms; Figure 1b) [16]. The sagittal qDESS images were used to generate axial and coronal reformats (Figure 1d-f). Sequence parameters of qDESS are described in Table 2.

Table 2. qDESS MRI sequence parameters

Sequence	qDESS
Matrix (RO × PE)	416×512
In-plane Resolution (mm2)	0.42×0.31
Slice Thickness (mm)	1.5
Number of Slices	80
TE S+, TE S- (ms)	5.7, 30.1
Number of Echoes	2
TR (ms)	17.9
Flip Angle (°)	20
Bandwidth (± kHz)	42
Parallel Imaging	2x1
% Corners Cut	25
Scan Time (mm:ss)	04:48

Abbreviations: qDESS = quantitative double-echo steady-state; MRI = magnetic resonance imaging; RO = readout; PE = phase encodes; TE = echo time; TR = repetition time

Structural analysis of knee OA (MOAKS scoring)

Structural, semi-quantitative assessment of cartilage and meniscus was performed using MOAKS [11] by the same researcher (SE). Both qDESS echoes with multiplanar reformatting

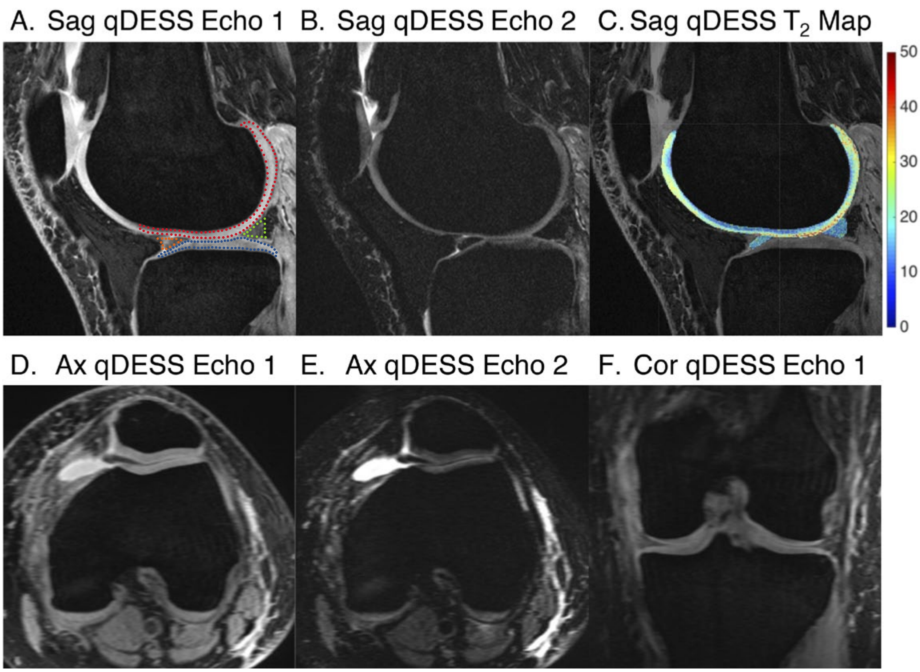

Figure 1. Representative example of (a) first and (b) second sagittal qDESS echo in 37-year-old female without OA, lateral compartment. In (a), femoral cartilage ROI is indicated by red dots, tibial cartilage ROI is indicated by blue dots, anterior meniscal horn is indicated by orange dots and posterior meniscal horn is indicated by green dots. (c) Corresponding T_2 colormaps of femoral cartilage and the anterior and posterior horn of the lateral meniscus (color bar on the right shows the range of T_2 values). Sagittal qDESS images are used to generate reformatted reconstructions in the (d, e) axial and (f) coronal plane. Abbreviations: Sag = sagittal; Ax = axial; Cor = coronal.

were used. Criteria for MOAKS grading for cartilage ($MOAKS_{cartilage}$) and meniscus ($MOAKS_{meniscus}$), used in this study, are described in Supplementary Material 1 and 2, respectively. We performed no second reading because high intra- and inter-observer reproducibility for MOAKS scoring using qDESS with separated echoes, especially for cartilage and meniscus, was reported in a previous study [16].

Quantitative MR analysis

The two echoes of qDESS were used to compute T_2 relaxation time parameter maps, by inverting the qDESS signal model [24]. qDESS T_2 measurements have shown to have high concordance with multi-echo spin echo T_2 measurements [25] and limited sensitivity to T_1 and signal to noise ratio variations in cartilage and meniscus [26]. The first echo (S+) of sagittal qDESS was used for manual segmentation of cartilage and menisci for the calculation of T_2 relaxation times (Figure 1c). Segmentation was performed on single slices, by the same researcher (SE) blinded for the patient's clinical data. For femoral and tibial cartilage segmentation, the centermost slice through the medial and lateral femoral condyle (defined as the slice midway between the slice on which the femoral condyle was first visible and the slice on which the femoral condyle was last visible) was identified. Four cartilage regions of interest (ROIs) were defined per patient: medial and lateral femoral cartilage as well as medial and lateral tibial cartilage. The trochlear cartilage was not included in quantitative analysis because of the potential influence of the magic angle effect on T_2 relaxation times in that specific region [27].

For meniscus segmentation, the sagittal slice depicting the maximum dimension of the anterior horn and posterior horn as individual triangles was used. Four meniscus ROIs were defined per patient: the anterior and posterior horn of the medial and lateral menisci. To avoid partial volume effects of joint fluid in case of a meniscal tear, the torn area was not included in segmentation. All segmentations and subsequent T_2 analyses were performed using custom in-house software created in MATLAB (version R2011b; The Math-Works).

Statistical analysis

We assessed the intra- and interobserver reproducibility for KLG scoring by calculating weighted Cohen's kappa's. Tests for normality of baseline characteristics and outcomes were performed using Shapiro-Wilk tests. Between-group differences in overall (i.e., pooled across all ROIs) T_2 values and MOAKS scores were evaluated using ANOVA (for parametric data) or Kruskal-Wallis tests (for non-parametric data). In case of statistically significant differences in mean age and/or sex among the three subject groups, a multivariate model with linear regression was used to assess the potential influence of these differences on T_2 values and MOAKS scores. Associations between radiographic OA and T_2 values and between radiographic OA and MOAKS were assessed in predefined cartilage and meniscus ROIs, and for overall scores using correlation analysis for ordinal variables (Spearman's correlation). Differences were considered statistically significant at $P < 0.05$. All statistical analyses were performed using SPSS (version 24.0.0.0, 2018).

RESULTS

Characteristics of study population

Out of the 196 potentially eligible patients, 53 subjects were included in this study: 20 subjects without knee OA, 18 subjects with mild knee OA, and 15 subjects with moderate knee OA. A flowchart of the selection of the study population is presented in Figure 2. Characteristics of study participants, stratified by degree of OA, are summarized in Table 3. There was a slight overall male predominance of 60%, yet no statistically significant differences in sex distribution were found across the three subject groups. The mean age of patients with mild and moderate OA was statistically significantly higher ($P < 0.001$) compared to subjects with no OA. No statistically significant association between age and T_2 values or MOAKS scores was found (data not shown).

Reproducibility of KLG scoring

Interobserver reproducibility for scoring the degree of radiographic knee OA according to KLG was good (weighted kappa: 0.78), while intra-observer reproducibility was excellent (weighted kappa: 0.85).

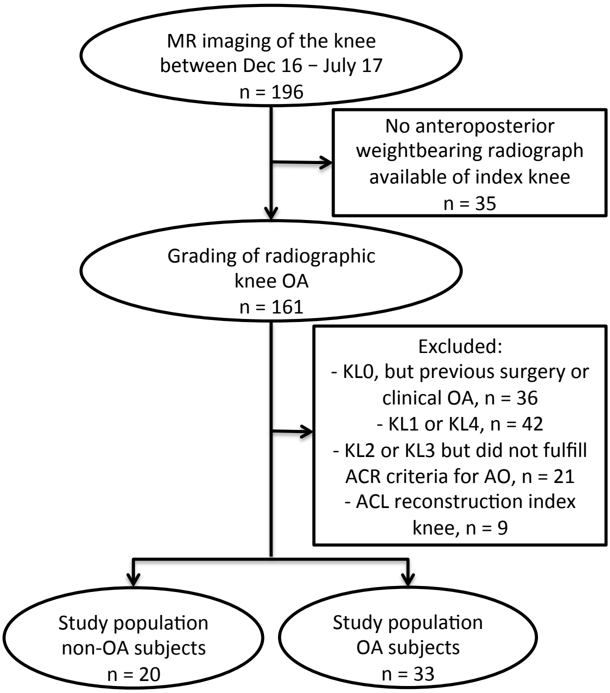

Figure 2. Flow-chart showing the selection process of the study population. In the rectangles on the right, the number and nature of exclusions is described. Abbreviations: MR = magnetic resonance; Dec = December; OA = osteoarthritis; KL = Kellgren and Lawrence grade; ACR = American College of Rheumatology; ACL = anterior cruciate ligament.

qDESS T_2 and MOAKS measurements in cartilage

Overall qDESS cartilage (i.e., pooled across all ROIs) T_2 values were 36.1 ± SD 4.3, 40.6 ± 5.9 and 47.1 ± 4.3 ms for no, mild, and moderate OA, respectively. The delta value (difference) in T_2 was 4.6 ms between no OA and mild OA and 6.5 ms between mild OA and moderate OA. Overall qDESS cartilage T_2 values were similar to T_2 values in previous literature (33.8-38.8, 34.9-41.8 and 40.5-46.9 ms for no, mild, and moderate OA, respectively [7,16,28]). Differences in qDESS T_2 values were statistically significant between the three subject groups ($P < 0.01$, Figure 3a).

Table 3. Characteristics of the study population

	No Knee OA	Mild Knee OA	Moderate Knee OA
All patients			
No. of patients	20	18	15
Age (y)[a]	34 ± 13	53 ± 13	59 ± 17
Female patients			
No. of patients	7 (35%)	6 (34%)	8 (53%)
Age (y)[a]*	38 ± 14	51 ± 14	62 ± 14
Male patients			
No. of patients	13 (65%)	12 (66%)	7 (47%)
Age (y)[a]*	32 ± 12	53 ± 14	54 ± 21

a: Mean values ± standard deviation

* There were statistically significant differences (P < 0.001) in age between the three subject groups

Abbreviations: OA = osteoarthritis; y = years

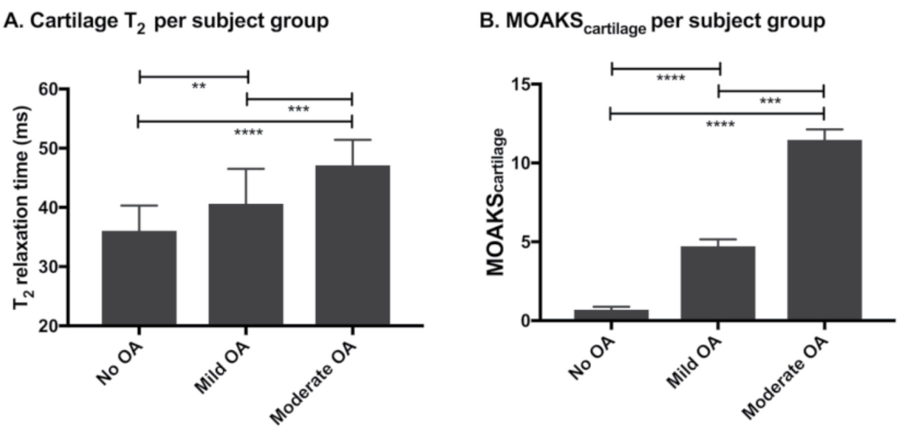

Figure 3. Discriminative power of quantitative and structural qDESS-based measurements in cartilage. Statistical significantly differences in (a) cartilage T_2 and (b) MOAKS$_{cartilage}$ scores were found among subject groups. Data is shown as overall mean values (pooled across all ROIs); vertical bars represent standard deviation. Horizontal bars represent statistically significance between two subject groups; ** = P < 0.01, *** = P < 0.001, **** = P < 0.0001. Abbreviations: ms = milliseconds; OA = osteoarthritis; ROI = region of interest.

Table 4. Cartilage T_2 values and $MOAKS_{cartilage}$ scores per ROI and overall scores, and their correlation with radiographic degree of OA

	No OA		Mild OA		Moderate OA		Correlation with radiographic OA[a]	
	T_2[b]	$MOAKS_{cartilage}$	T_2[b]	$MOAKS_{cartilage}$	T_2[b]	$MOAKS_{cartilage}$	T_2[b] vs. KLG	MOAKS vs. KLG
Cartilage ROI:	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Rho (95%-CI)*	*Rho (95%-CI)*
Medial femur	36.5 ± 5.0	0.4 ± 0.7	43.4 ± 6.1	1.7 ± 1.5	50.6 ± 7.2	3.5 ± 2.9	0.71 (0.53-0.82)	0.62 (0.42-0.77)
Lateral femur	37.2 ± 4.4	0.3 ± 0.7	40.8 ± 5.4	1.3 ± 1.2	48.8 ± 8.4	2.4 ± 2.7	0.57 (0.35-0.73)	0.50 (0.26-0.69)
Medial tibia	34.7 ± 3.7	0.1 ± 0.2	39.4 ± 5.8	1.1 ± 2.4	44.2 ± 6.7	3.4 ± 3.7	0.53 (0.30-0.71)	0.51 (0.28-0.69)
Lateral tibia	35.8 ± 5.0	0.0 ± 0.0	38.8 ± 6.3	0.6 ± 1.2	44.8 ± 8.6	2.2 ± 2.8	0.43 (0.17-0.63)	0.51 (0.28-0.69)
Cartilage overall[c]	36.0 ± 4.3	0.7 ± 0.2	40.6 ± 5.9	4.7 ± 0.4	47.1 ± 4.3	11.5 ± 0.7	0.75 (0.60-0.85)	0.82 (0.70-0.89)

a: Data is shown as Spearman's Rho correlation coefficient between KLG and corresponding T_2 or MOAKS score, with 95% confidence interval shown between brackets
b: In milliseconds (ms)
c: Pooled across all ROIs
Abbreviations: ROI = region of interest, KLG = Kellgren Lawrence grade, OA = osteoarthritis, SD = standard deviation, 95%-CI = 95% confidence interval

Likewise, overall $MOAKS_{cartilage}$ scores were consistently higher with increasing stages of OA with statistically significant differences found between the three subject groups ($P < 0.001$; Figure 3b). The delta value (difference) in $MOAKS_{cartilage}$ was 4 between no OA and mild OA and 6.8 between mild OA and moderate OA. A representative example of qDESS $MOAKS_{cartilage}$ findings in a subject with moderate OA, compared to a corresponding fat-suppressed T_2-weighted image, is provided in Figure 4. Osteophytes were not included in the analyses of the present study, but they were identified on qDESS images. Subchondral cysts and surrounding bone marrow lesions (BMLs) were not included in the analyses of this study but identified as well (see Figure 4). Overall qDESS T_2 and MOAKS scores for cartilage, stratified by degree of OA, are summarized in Table 4.

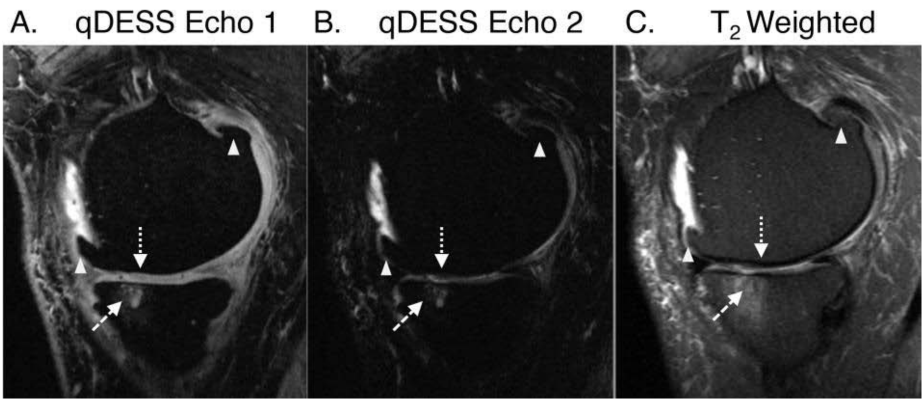

Figure 4. Example of $MOAKS_{cartilage}$ assessment in 71-year-old male with moderate OA on (a, b) qDESS images, compared to (c) corresponding fat-suppressed T_2-weighted image (TE 54 ms; flip angle 142°; FOV 14 cm; matrix 384x192). Sagittal images of (a) first and (b) second qDESS echo show thinning of medial femoral cartilage (dotted arrow). Subchondral cysts and surrounding BML (dashed arrow) and osteophytes (triangles) were not included in the analysis of the present study, but they were identified on qDESS images. Note the underestimation of BML size on qDESS images compared to T_2-weighted image. Abbreviations: OA = osteoarthritis; BML = bone marrow lesion.

qDESS T_2 and MOAKS measurements in menisci

In menisci, overall (i.e., pooled across all ROIs) qDESS T_2 values were 15 ± SD 3.6, 17.5 ± 3.8 and 20.6 ± 4.7 ms for no, mild, and moderate OA, respectively. The delta value (difference) in T_2 was 2.5 ms between no OA and mild OA and 3.1 ms between mild OA and moderate OA. Overall qDESS meniscus T_2 values were similar to T_2 values in previous studies (11.4-21.3, 13.5-22.4 and 16.8-24.2 ms for no, mild, and moderate OA, respectively [7,16,29]). Differences in qDESS T_2 values were statistically significant between the three subject groups ($P < 0.01$; Figure 5a).

Differences in qDESS $MOAKS_{meniscus}$ scores were statistically significant between the three subject groups ($P < 0.001$; Figure 5b), except for the difference in $MOAKS_{meniscus}$ scores between subjects with mild and moderate OA. The delta value (difference) in $MOAKS_{meniscus}$ was 2.2 between no OA and mild OA and 1.5 between mild OA and moderate OA. An example of qDESS $MOAKS_{meniscus}$ assessment in a subject with mild OA, compared to a corresponding proton density-weighted image, is provided in Figure S1. Overall qDESS T_2 values and MOAKS scores for menisci, stratified by degree of OA, are summarized in Table 5.

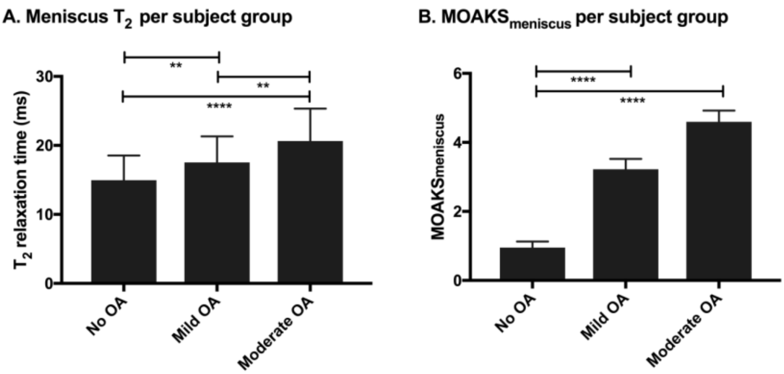

Figure 5. Discriminative power of quantitative and structural qDESS-based measurements in menisci. Statistical significantly differences in (a) meniscus T_2 and (b) $MOAKS_{meniscus}$ scores were found among subject groups. Data is shown as overall mean values (pooled across all ROIs); vertical bars represent standard deviation. Horizontal bars represent statistically significance between two subject groups; ** = P < 0.01, *** = P < 0.001, **** = P < 0.0001. Abbreviations: ms = millisecond; OA = osteoarthritis; ROI = region of interest.

With regard to meniscus extrusion, the presence of meniscus extrusion was consistent with the degree of OA. We found a medial extrusion of 0.3 ± SD 0.1, 0.9 ± 0.3 and 1.1 ± 0.3 in non-OA subjects, subjects with mild OA, and subjects with moderate OA, respectively. A lateral extrusion of 0.0 ± SD 0.0, 0.4 ± 0.2 and 0.7 ± 0.3 was found in non-OA subjects, subjects with mild OA, and subjects with moderate OA, respectively. Statistically significant differences in medial and lateral extrusion grade were found among the three subject groups (P = 0.04 and P = 0.03 for medial and lateral extrusion, respectively).

qDESS T_2 and MOAKS in cartilage and meniscal ROIs

qDESS T_2 values and MOAKS scores for each cartilage and meniscus ROI, stratified by degree of OA, are summarized in Table 4 and Table 5, respectively. In all cartilage and meniscus ROIs, statistically significant correlations were found between qDESS T_2 values and radiographic OA and between MOAKS scores and radiographic OA. The strongest correlation (*r* = 0.71) between MRI findings and radiographic OA was found in the medial femoral cartilage, the weakest correlation (*r* = 0.29) was found in the anterior horn of the medial meniscus.

Table 5. Meniscus T_2 values and MOAKSmeniscus scores per ROI and overall scores, and their correlation with radiographic degree of OA

	No OA		Mild OA		Moderate OA		Correlation with radiographic OA[a]	
	T_2[b]	MOAKSmeniscus	T_2[b]	MOAKSmeniscus	T_2[b]	MOAKSmeniscus	T_2[b] vs. KLG	MOAKS vs. KLG
Meniscus ROI:	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Mean ± SD*	*Rho (95%-CI)*	*Rho (95%-CI)*
Medial anterior	14.2 ± 2.4	0.1 ± 0.4	16.1 ± 2.5	0.4 ± 1.1	17.7 ± 5.2	0.7 ± 1.2	0.39 (0.13-0.60)	0.29 (0.02-0.53)
Medial posterior	16.3 ± 5.9	0.5 ± 0.9	19.6 ± 4.8	1.1 ± 1.2	22.9 ± 7.6	1.3 ± 1.2	0.50 (0.25-0.68)	0.34 (0.07-0.57)
Lateral anterior	14.8 ± 3.5	0.2 ± 0.7	17.2 ± 3.8	1.1 ± 1.0	20.6 ± 5.3	1.3 ± 1.5	0.51 (0.27-0.69)	0.45 (0.19-0.65)
Lateral posterior	14.6 ± 2.4	0.2 ± 0.7	17.2 ± 4.0	0.7 ± 1.0	21.2 ± 7.9	1.3 ± 1.0	0.48 (0.23-0.67)	0.52 (0.29-0.70)
Meniscus overall[c]	15.0 ± 3.6	1.0 ± 0.2	17.5 ± 3.8	3.2 ± 0.3	20.6 ± 4.7	4.6 ± 0.3	0.64 (0.44-0.78)	0.65 (0.45-0.79)

a: Data is shown as Spearman's Rho correlation coefficient between KLG and corresponding T_2 or MOAKS score, with 95% confidence interval shown between brackets
b: In milliseconds (ms)
c: Pooled across all ROIs
Abbreviations: ROI = region of interest, KLG = Kellgren Lawrence grade, OA = osteoarthritis, SD = standard deviation, 95%-CI = 95% confidence interval

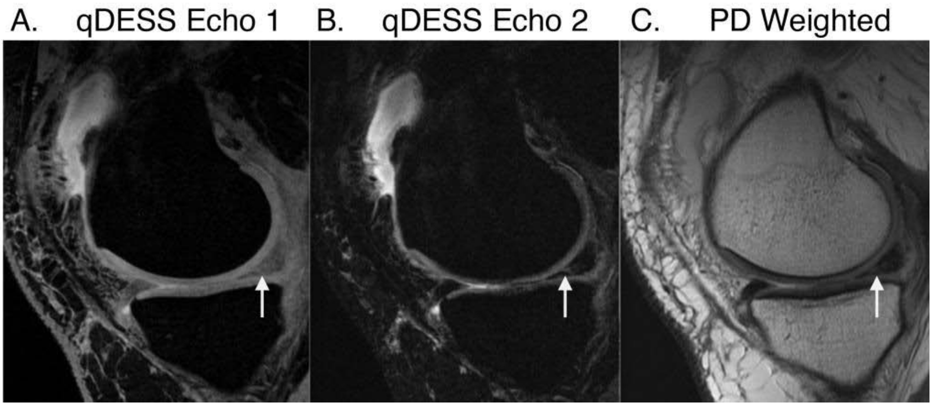

Figure S1. Example of $MOAKS_{meniscus}$ findings in 47-year-old male with mild OA, on sagittal images of (a) first and (b) second qDESS echo, compared to (c) corresponding proton density-weighted image (TE 35 ms; flip angle 142°; FOV 14 cm; matrix 384x224), showing a complex tear (solid arrow) in the posterior horn of the medial meniscus. $MOAKS_{meniscus}$ scoring in the present study included meniscus signal, tears, and (partial) maceration. The second qDESS echo especially was useful in identifying meniscus pathology. Abbreviations: OA = osteoarthritis; PD = proton density.

DISCUSSION

In the present study, we demonstrated that quantitative and structural measurements in cartilage and meniscus, obtained with a single 5-minute qDESS sequence, can differentiate between OA stages. T_2 values in cartilage and menisci were similar to T_2 values reported in previous studies [5-8].

The disease distribution of OA within the knee joint is often compartmental, with high variability regarding compartmental involvement [6,20,21]. Therefore, we assessed the validity of qDESS-based biomarkers in various cartilage and meniscus ROIs. The discriminative power to distinguish degree of OA was the greatest in the medial femoral cartilage, and the least in the anterior horn of the medial meniscus. These findings were most likely caused by the uneven distribution of OA features; the anterior horn of the medial meniscus showed relatively low T_2 values and MOAKS scores in subjects with mild or moderate OA while the medial femoral cartilage showed relatively high T_2 values and MOAKS scores in those subjects. Despite the differences in discriminative power, T_2 values and MOAKS outcomes in all ROIs were found to be statistical significantly correlated with radiographic knee OA.

The qDESS sequence in the present study was optimized to simultaneously generate high resolution images and quantitative measurements, by combining high spatial resolution with high SNR, in one single, rapid scan. While twice as fast, the resolution and voxel volume of this qDESS sequence (0.18µL) was over 10x better than the resolution of established quantitative T_2 sequences [7,30]. In a previous study, qDESS has shown high T_2 accuracy compared to multi-echo spin echo sequences, as well as high accuracy for MOAKS measurements compared to conventional spin echo based sequences, with high intra- and inter-observer reproducibility [16,25]. qDESS has been thought to underestimate the size of bone marrow lesions (BMLs), which seems to be the case in our study as well (see Figure 4, not studied), likely due to T_2* susceptibility effects [15]. A separation of the two qDESS echoes may enhance accuracy of BML detection compared to previous qDESS studies [31]. Although outside the scope of this study, further work is needed to test and optimize BML detection with qDESS.

Building upon the work of Chaudhari et al. [16], the present study assesses the discriminative power of a 5-minute qDESS sequence to obtain T_2 values and MOAKS in a clinical knee OA population. We validated T_2 measurements and MOAKS against radiographic OA, which remains the gold imaging standard for diagnosing and monitoring knee OA [18,19]. In OA research, KLG2 is considered the cut-off point for the presence of radiographic knee OA [4,18,19,32]. Although potentially a relevant group in the context of early OA imaging, we did not include patients with KLG1, indicating doubtful radiographic OA. The reproducibility of scoring KLG1 (i.e., doubtful narrowing of joint space and possible osteophytic lipping) is relatively poor, most likely due to differences in the interpretation of radiographic findings, especially concerning osteophytic lipping [18]. Also, patients with severe radiographic OA (i.e. KLG4) were not included in the present study, as bony deformity and bone-to-bone contact precludes accurate segmentation of cartilage.

OA is among the top ten burdensome diseases, with the knee being the most affected joint [1]. In the light of increased numbers associated MR imaging studies [2,33], reducing MR imaging acquisition time is highly relevant. Reducing scan time saves costs and increases patient comfort and may reduce motion artifacts in longer acquisitions [16]. Because qDESS rapidly provides rich structural and quantitative information, there is a great promise for using this technique in large clinical OA studies. Recent advances in deep learning and simultaneously imaging both knees with qDESS may further reduce scan time, without loss of image quality or quantitative accuracy [34-36].

This study has some limitations that must be acknowledged. First, segmentation of quantitative analysis and MOAKS scoring was performed by a single, experienced researcher. As evidence of high intra- and inter-observer reproducibility for cartilage and meniscus segmentation and MOAKS assessment with qDESS images has been reported previously [16], analyses performed by a single researcher was considered sufficient. Second, our validation study was cross-sectional. The lack of a longitudinal aspect may limit interpretation regarding the potential use of qDESS in clinical trials. Therefore, future studies on the sensitivity of qDESS-based biomarkers for longitudinal changes in the knee are required. Third, KLG was used as reference standard, which is considered the gold standard for imaging-based knee OA classification [4]. Radiographically detected joint space narrowing (JSN) is currently the only structural endpoint accepted by the European and US regulatory bodies (European Medicines Agency and FDA) to assess knee OA progression [37] and is commonly used in qMRI validation studies [6,7]. We opted for this method because we aimed to explicitly use qDESS in a clinically relevant matter. However, an important drawback of the KLG method is the low reproducibility of JSN measures reported in literature, in particular in longitudinal assessment of knee OA [4,38]. Given the cross-sectional design of our study without longitudinal measures, challenges concerning longitudinal KLG measures are unlikely. To optimize reproducibility, we used standardized radiographs (weight-bearing AP). To assess reproducibility, both inter- and intra-observer reproducibility of KLG were carefully evaluated in the present study (weighted kappa of 0.78 and 0.85 for inter- and intra-observer reproducibility respectively). Finally, although osteophytes and BMLs are important OA features, they were not studied. The primary objective of this study was to assess the validity of qDESS for cartilage and menisci in OA subjects. We focused on those tissues as they have conclusively been shown to be strong indicators for OA and because of their possibilities in both quantitative (T_2) and semi-quantitative (MOAKS) [4,7,8,11,39]. To assess the external validity of our study results, further studies evaluating other relevant OA features will be essential, in particular regarding BML detection. In addition, future validation studies on qDESS T2 values in OA patients against histological degree of degeneration (the gold standard for tissue changes) are desirable.

In conclusion, quantitative T_2 and structural assessment of cartilage and meniscus with a single 5-minute qDESS scan can distinguish between different grades of OA and show significant correlations with the reference standard. These results demonstrate the potential of qDESS as an efficient and accurate imaging tool for OA research.

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SUPPLEMENTARY MATERIAL 1: MOAKS GRADING FOR CARTILAGE

For structural, semi-quantitative assessment of cartilage in the present study, cartilage sub-scores ($MOAKS_{cartilage}$), directly derived from the MOAKS total scores, were used (described in Table S1). $MOAKS_{cartilage}$ includes the size of cartilage lesions and the percentage of cartilage lesions being full thickness [1].

Table S1. MOAKS grading for cartilage

Findings on MR images	MOAKS score for % full thickness	MOAKS score for size of cartilage lesions	MOAKS cartilage score[a]
Normal	0	0	0
1–10% of the cartilage area damaged No full-thickness cartilage loss	0	1	1
1–10% of the cartilage area damaged 1–10% full-thickness cartilage loss	1	1	2
10-75% of the cartilage area damaged No full-thickness cartilage loss	0	2	2
10-75% of the cartilage area damaged 1-10% full-thickness cartilage loss	1	2	3
10-75% of the cartilage area damaged 10-75% full-thickness cartilage loss	2	2	4
>75% of the cartilage area damaged No full-thickness cartilage loss	0	3	3
>75% of the cartilage area damaged 1-10% full-thickness cartilage loss	1	3	4
>75% of the cartilage area damaged 10-75% full-thickness cartilage loss	2	3	5
>75% of the cartilage area damaged >75% full-thickness cartilage loss	3	3	6

a: MOAKScartilage score is the sum of MOAKS score for % full thickness and MOAKS score for size of cartilage lesions
Abbreviations: MR = magnetic resonance

SUPPLEMENTARY MATERIAL 2: MOAKS GRADING FOR MENISCUS

For structural, semi-quantitative assessment of the meniscus in the present study, meniscus subscores ($MOAKS_{meniscus}$) based on MOAKS total scores were used, including meniscus signal, tears, and (partial) maceration (described in Table S2). The rationale behind $MOAKS_{meniscus}$ criteria and the hierarchy in $MOAKS_{meniscus}$ scoring used in the present study was based on the clinical important effects these meniscus findings have as described in literature [2; 3]

Table S2. MOAKS grading for meniscus

Findings on MR images	**MOAKSmeniscus score**
Normal meniscus	0
Signal	1
Non-complex tear and/or meniscal cyst	2
Complex tear and/or partial maceration	3
Complete maceration	4
Extrusion findings on MR images[a]	**MOAKS extrusion score**
< 2 mm	0
2-2.9 mm	1
3-4.9 mm	2
> 5 mm	3

a: Measured on coronal image, excluding osteophytes
Abbreviations: MR = magnetic resonance

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