T_2 mapping of knee cartilage: multicenter multivendor reproducibility

SM Eijgenraam, J Verschueren, S Klein, DHJ Poot, SMA Bierma-Zeinstra,
JA Hernandez Tamames, PA Wielopolski, M Reijman, EHG Oei

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ABSTRACT

Objective: T_2 mapping is increasingly used to quantify cartilage degeneration in knee osteoarthritis, yet multicenter reproducibility studies of cartilage T_2 mapping are limited. The purpose of this study was to determine the longitudinal reproducibility and multicenter comparability of cartilage T_2 mapping, using various MRI equipment and acquisition protocols.

Methods: In this prospective multicenter study, four traveling, healthy human subjects underwent T_2 mapping twice at five different centers, over a 6-month-interval. Centers had various MRI scanners, field strengths, and T_2 mapping acquisition protocols. Mean T_2 values were calculated in six cartilage regions of interest (ROIs). A T_2 phantom was scanned once at each center. To evaluate longitudinal reproducibility, ICC, RMS-CV, and Bland-Altman plots were used. To assess comparability of in vivo and phantom T_2 values across centers, ANOVA was performed.

Results: ICCs of overall T_2 measurements (all centers pooled), in each ROI ranged from 0.73 to 0.91, indicating a good to excellent longitudinal reproducibility. RMS-CVs in each ROI ranged from 1.1% to 1.5%. The overall RMS-CV (all ROIs pooled) in each center ranged from 0.6% to 1.6%. Bland-Altman plots revealed that none of the centers showed a systematic error. Significant differences in absolute T_2 values were observed across centers, both in vivo and in the phantom.

Conclusion: The results of this study indicate that T_2 mapping can be used to longitudinal assess cartilage degeneration in multicenter studies. Given the differences in absolute cartilage T_2 values across centers, absolute T_2 values derived from various centers in multicenter multivendor trials should not be pooled.

INTRODUCTION

Quantitative magnetic resonance imaging (qMRI) techniques to assess changes in biochemical cartilage composition in osteoarthritis (OA) are emerging [1]. By detecting cartilage degeneration before it is visible on radiography or conventional MRI, qMRI techniques enable early intervention and monitoring of disease progression in OA [2]. T_2 mapping, which provides a marker for collagen integrity without the need for intravenous contrast or specific MRI hardware [2-5], is the most widely used qMRI technique in knee OA research [5,6].

Although cartilage T_2 mapping has found wide-spread use in OA research [7], reproducibility studies on T_2 mapping in a multicenter setting are scarce. Longitudinal reproducibility analyses of multicenter cartilage T_2 mapping have been limited to studies using similar scanners and harmonized MRI acquisition protocols [5,8,9]. However, differences in MRI hardware and T_2 mapping sequences, which may be attributable to local requirements and restrictions regarding MRI acquisition, are often present when performing a multicenter trial. Complete standardization of MRI acquisition across different centers is therefore, not always feasible, especially in large-scale multidisciplinary clinical trials. Little is known about the longitudinal reproducibility of cartilage T_2 values acquired on MRI scanners from different vendors and non-harmonized acquisition protocols.

The aim of the present study was to evaluate the multicenter reproducibility of cartilage T_2 mapping, from a clinical and pragmatic perspective. We assessed the longitudinal reproducibility and multicenter comparability of T_2 mapping of different cartilage regions, using various MRI systems, field strengths and acquisition protocols.

METHODS

Study design

In this prospective observational study, five medical centers located in different geographical parts of The Netherlands participated. In these centers, a multicenter randomized controlled trial is currently conducted, in which T_2 mapping is used as an outcome measure for deterioration of knee cartilage two years after a meniscal tear. Four traveling human subjects underwent MR imaging of the knee, including a T_2 mapping sequence, at each of the five centers in one day (i.e. baseline measurements). To evaluate longitudinal reproducibility of T_2 mapping, the exact same experiment was performed six months later (i.e. follow-up measurements). Subjects were scanned in the same order in each center, both at baseline and follow-up. Moreover, centers were visited in the same order and at the same time of day to address potential diurnal variation in T_2 measurements.

To assess comparability of T_2 values across centers, cross-validation was performed at baseline in human subjects as well as a phantom. Approval from the Institutional Review

Board of our institution [number deleted to maintain the integrity of the review process]. and written consent of all subjects was obtained.

Human subjects and phantom

For in vivo T_2 measurements, the left knee of four healthy volunteers (median age 29 years, range 25-30 years, median BMI 21.5 kg/m^2, three females) was scanned. The subjects had no history of knee pathology and did not report any knee complaints or injuries before or during the 6 months between scans. During baseline- and follow-up measurement days, subjects all had the same physical activity level without significant exercise or heavy loading. The subjects traveled by car; the same car was used during baseline- and follow-up measurements. None of the subjects engaged in significant exercise or heavy loading of the knee two days preceding the measurement days. An in-house developed phantom was scanned once at each center for cross-validation of T_2 values. The phantom consisted of eight vials of 3 cm diameter, containing various concentrations of manganese chloride (0 to 80 mg/ml). These concentrations were selected to encompass T_2 values within the range of human articular cartilage [1]. Phantom stability was verified (ICC 0.90, 95%-CI [0.856–0.928] over a 5-month-interval).

Data acquisition

MRI acquisition parameters, stratified per center, are summarized in Table 1. MRI scanners manufactured by GE Healthcare (Milwaukee, WI, USA), Siemens (Erlangen, Germany) and Philips (Eindhoven, The Netherlands) were used for this study; three 3-Tesla scanners (GE, Siemens and Philips), and two 1.5-Tesla scanners (both Siemens). Dedicated knee coils were used in each center; either receive only or combined transmit–receive. MRI protocols were optimized in each center according to locally available MRI hardware and software. All knees were scanned in the sagittal plane. For phantom measurements, the same T_2 mapping protocol was used as for human subjects. For the purpose of cartilage segmentation *in vivo*, a sagittal high-resolution fast-spoiled gradient-echo (FSPGR) sequence with fat-saturation was acquired of each subject at center 1 at baseline. None of the MRI systems or acquisition protocols underwent updates or adjustments during the study period.

Image processing

An in-house developed MATLAB (R2011a; The Math-Works, Natick, MA, USA) extension was used for post-processing analyses of all scans [10]. Rigid registration in 3D provided motion compensation between echo times of the T_2 mappings scans. All T_2 mapping scans were registered to the high-resolution FSPGR scan acquired at baseline at center 1, to ensure that exactly matching regions of interest (ROIs) were measured. Full-thickness cartilage masks of the central portion of the medial and lateral tibiofemoral compartment were manually segmented on the subjects' high-resolution FSPGR scans. Segmentation was performed by

a researcher with a medical degree and four years of experience in musculoskeletal imaging [initials deleted to maintain the integrity of the review process]. on five slices with a three-millimeter-interval. Subsequently, the segmented masks were divided into six cartilage ROIs, located in the medial and lateral weight-bearing and posterior femoral condyles and tibial plateaus (Figure 1). The outer perimeters of the menisci demarcated the weight-bearing ROIs of the femur and tibia. The posterior ROIs contained the femoral cartilage behind the posterior border of the menisci. Within each ROI, mean T_2 relaxation time was computed using a weighted averaging procedure [10]. The automated registration of the T_2 mapping scan to the high-resolution scan at follow-up yielded visually inaccurate registration in two measurements (center 3; subject 3 and center 4; subject 4). For these measurements, cartilage was segmented directly on T_2 mapping images while ensuring that the regions matched those segmented on the high-resolution scan. In phantom scans, a central circle of approximately 2 cm diameter was segmented directly on the T_2 mapping images, on four consecutive slices of 3 mm thickness.

Table 1. MRI sequence parameters

	Center 1	**Center 2**	**Center 3**	**Center 4**	**Center 5**
Scanner	3-T Discovery MR750, GE Healthcare, Milwaukee, WI, United States	1.5-T Aera, Siemens, Erlangen, Germany	1.5-TAera, Siemens, Erlangen, Germany	3-T Skyra, Siemens, Erlangen, Germany	3-T Achieva dStream, Philips Healthcare, Best, The Netherlands
Sequence type	3D Fast Spin Echo FS	2D Spin Echo non-FS	2D Spin Echo non-FS	2D Spin Echo FS	2D Fast Spin Echo FS
Matrix (RO x PE)	288 x 192	192 x 144	256 x 256	256 x 190	300 x 247
Slice thickness/spacing	3/0	3/0.2	3/0.3	3/0.4	3/0.3
Number of slices	36	28	30	27	40
Number of echoes	5	8	6	8	9
TE (ms)	3; 13; 27; 41; 68	8; 16; 24; 32; 40; 48; 56; 64	14; 28; 41; 55; 69; 83	9; 17; 26; 34; 43; 51; 60; 68	7; 15; 23; 29,37; 44; 51; 58; 66
TR (ms)	1263	2000	2690	2170	3582
FOV (cm)	15	18	16	18	15
Coil	8-channel S&R rigid	15-channel S&R rigid	15-channel S&R rigid	15-channel S&R rigid	8-channel knee R rigid
Scan Time (mm:ss)	09:41	3.06	07:15	06:27	08:31

Abbreviations: RO = readout, PE = phase encoding, TE = echo time, TR = repetition time, FOV = field of view, FS = fat suppression, S&R = send and receive, R = Receive

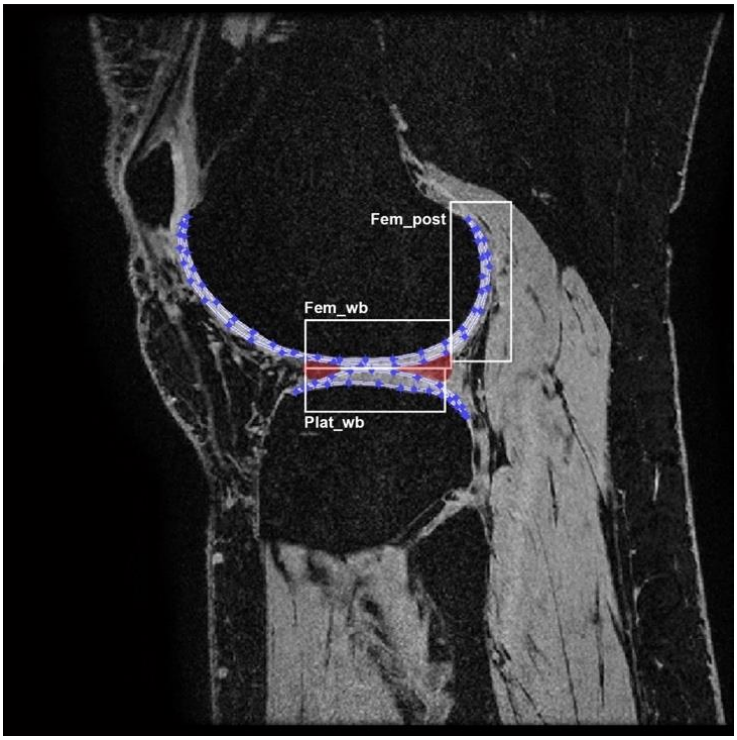

Figure 1. Cartilage segmentation on sagittal high-resolution FSPGR image, lateral compartment. Blue dotted lines surround the segmented mask; white boxes represent the ROIs. Abbreviations: Fem_post = posterior femoral condyle; Fem_wb = weight-bearing femoral condyle; Plat_wb = weight-bearing tibial plateau; FSPGR = fast spin gradient echo; ROI = region of interest.

Statistical analysis

The longitudinal reproducibility of T_2 measurements in each cartilage ROI was evaluated with intraclass correlation coefficients (ICCs) for absolute agreement of single measures, using a two-way random model, by pooling the T_2 values of all subjects from all centers. To interpret ICC findings, we used the following scale: poor (ICC < 0.5), moderate (ICC 0.5-0.7), good (ICC 0.7-0.9), or excellent (ICC > 0.9) reproducibility [11].

In addition, we calculated coefficients of variation (CVs, defined as the standard deviation (SD) normalized by the mean value of the measurements) of differences in T_2 measurements between baseline and follow-up for each subject. Since averaging the subject's CVs to obtain pooled CVs for each center and for each cartilage ROI is inadequate [12,13], we calculated the root-mean-square coefficient of variation (RMS-CV, expressed as a percentage) according to the method of Gluer et al. [12]. RMS-CV is defined as the square root of the sum of the squared CVs for each subject, divided by the sample size. An RMS-CV value of zero represents a perfect precision of agreement. Bland-Altman plots were obtained for each center to determine

limits of agreement of T_2 measurements, in order to gain insight into the extent and nature of the error (i.e. systematic or random error), and to identify possible outliers. The limits of agreement were defined as the mean difference in T_2 values between baseline and follow-up measurements (i.e. the mean error) ± 1.96 SD. The smaller the range between these two limits, the higher the reproducibility.

For cross-validation of T_2 mapping across centers, we calculated pooled T_2 values from all subjects, as well as phantom T_2 values, for each center. Data was tested for normality using Shapiro-Wilk tests. Between-center differences in T_2 values were analyzed using one-way ANOVA with Dunn's Multiple Comparison Test. P values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 24.0 (IBM Corp, Armonk, NY, USA, 2016) and GraphPad Prism version 8.0 (GraphPad Software, San Diego California USA, 2018).

RESULTS

Longitudinal reproducibility of *in vivo* T_2 measurements

Mean T_2 values and longitudinal reproducibility outcomes of human subjects for each cartilage ROI are presented in Table 2. ICCs of T_2 measurements pooled across all centers ranged from 0.73 to 0.91 for the different ROIs, indicating a good to excellent reproducibility. When pooling the longitudinal T_2 values of all ROIs across all centers, we found an excellent reproducibility (ICC 0.90, 95% confidence interval [0.856–0.928]). The RMS-CVs in each ROI ranged from 1.1% to 1.5%, Bland-Altman plots of these measurements showed

Table 2. In vivo T2 values and longitudinal reproducibility per cartilage ROI

	Baseline		6-months FU		Agreement		
	T2† (ms)	CI-95	T2† (ms)	CI-95	ICC‡	CI-95	RMS-CV (%)
Femoral cartilage							
Weight-bearing							
Medial	46.3	42.6 - 50.0	47.2	43.1 - 51.3	0.91	0.78 - 0.96	1.3
Lateral	47.9	44.4 - 51.4	48	44.6 - 51.3	0.82	0.59 - 0.92	1.3
Posterior							
Medial	47	43.5 - 50.4	46	42.5 - 49.6	0.91	0.80 - 0.97	1.1
Lateral	43.9	40.1 - 47.7	42.8	39.7 - 45.8	0.85	0.66 - 0.94	1.2
Tibial cartilage							
Medial	40.8	38.0 - 43.6	41.9	37.9 - 45.8	0.86	0.69 - 0.94	1.4
Lateral	34.5	32.3 - 36.7	35.2	32.8 - 37.5	0.73	0.44 - 0.89	1.5

† Mean T2 relaxation times of human volunteers, pooled across all centers

‡ intraclass correlation coefficient of absolute agreement, single measurements

Abbreviations: ROI = region of interest, FU = follow-up, ICC = Intraclass Correlation Coefficient, CI-95 = 95% confidence interval, RMS-CV = root mean square coefficient of variation

Table 3. RMS-CV of longitudinal in vivo T2 measurements per cartilage ROI

	Center 1	Center 2	Center 3	Center 4	Center 5
Femoral cartilage					
Weight-bearing					
Medial	1.6	3.4	5.2	1.2	0.9
Lateral	3.3	2.2	3.3	4.2	1.3
Posterior					
Medial	1.5	4.0	2.3	1.2	2.0
Lateral	1.1	6.2	2.4	2.9	1.1
Tibial cartilage					
Medial	2.7	1.8	4.0	4.5	1.4
Lateral	2.8	1.2	2.7	6.2	1.1
Overall (all ROIs pooled)	1.1	1.3	1.4	1.6	0.6

Note: RMS-CV shows the precision of agreement for longitudinal T2 measurements in human subjects, shown as percentage. The lower the RMS-CV, the higher the precision. Abbreviations: RMS-CV = root mean square coefficient of variation, ROI = region of interest

no systematic error (data not shown). Table 3 summarizes the RMS-CVs of longitudinal T_2 measurements per center. The overall (all ROIs pooled) RMS-CV in each center ranged from 0.6% to 1.6%. Bland-Altman plots for each center revealed mean differences between overall (all ROIs pooled) baseline and follow-up T_2 measurements ranging from 0.03 to 2.70 ms (Figure 2). Lowest mean differences and narrowest confidence intervals were observed in center 1 and center 5, indicating highest reproducibility. None of the centers showed a systematic error.

Two (out of 120) data points of the follow-up measurements were excluded from analysis. The lateral posterior femoral condyle of subject 1 in center 2 and the lateral tibial plateau of subject 4 in center 3 showed T_2 values beyond plausible ranges (> 150 ms). The invalid T_2 value of the first mentioned ROI was due to substantial excess blurring in the slice direction in that particular scan. Non-saturated fat signals, causing partial volume effects, were most likely responsible for the invalid value of the other excluded ROI.

Multicenter comparability of *in vivo* and phantom T_2 measurements

In Figure 3-A, T_2 values of all cartilage ROIs pooled are plotted per center, showing discrepancies in pooled T_2 values across centers. A statistically significant difference in pooled T_2 values was found between center 1 and center 4 ($P < 0.01$). However, mutual differences in T_2 values between subjects were consistent across all centers (Figure 3-A). An identical pattern of mutual differences in T_2 values among subjects was observed at follow-up (data not shown). Moreover, phantom T_2 measurements showed a comparable pattern of differences in T_2 values across centers as seen *in vivo*, especially in vials with lower concentration of manganese chloride (Figure 3-B).

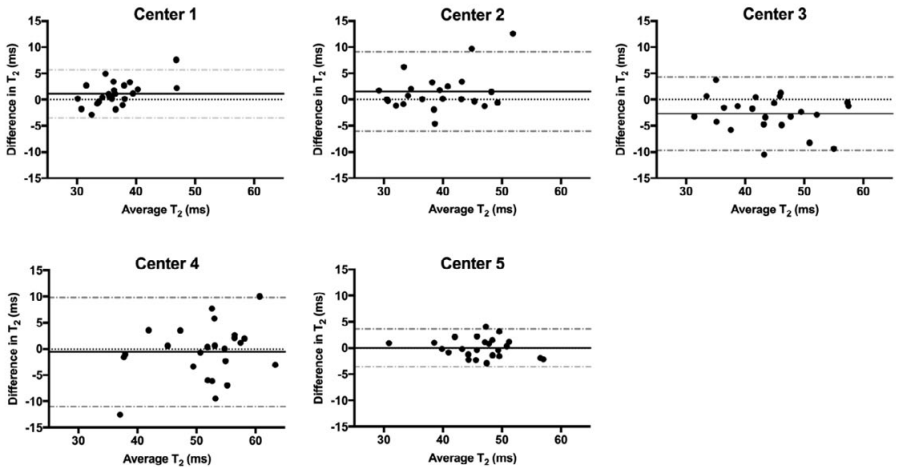

Figure 2. Bland-Altman plots showing the differences in *in vivo* T_2 values between baseline and follow-up against the mean T_2 values in each center. The bold line represents the mean difference, dotted lines represent limits of agreement. Note the pattern and dispersion of the black dots in relation to the mean difference in each center, indicating a random error rather than than a systematic error, and the differences in limits of agreement across centers. The narrower the limits, the higher the reproducibility of measurements.

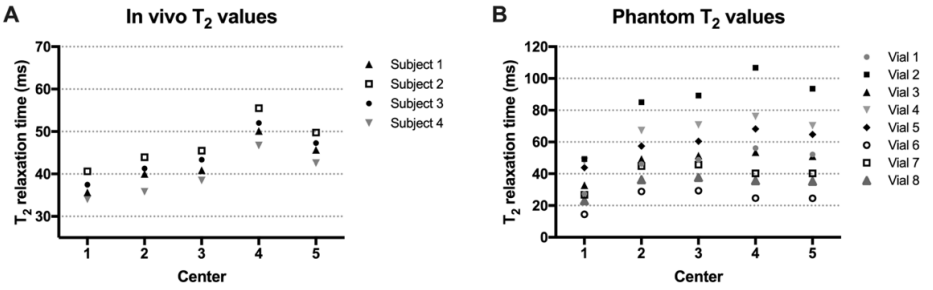

Figure 3. Mean T_2 values pooled across all cartilage regions of interest (ROIs), acquired at baseline. A) *In vivo* T_2 values plotted per subject for each center. B) Phantom T_2 values plotted per vial for each center. The concentration of manganese chloride for each vial was: vial 1 = 0%; vial 2 = 5%; vial 3 = 10%; vial 4 = 15%; vial 5 = 20%; vial 6 = 30%; vial 7 = 50%; and vial 8 = 80%.

DISCUSSION

The reproducibility of qMRI techniques such as T_2 mapping is a highly relevant issue that multicenter studies are facing. In the present study, we evaluated the longitudinal reproducibility and comparability of T_2 measurements in different cartilage ROIs in a multicenter setting, using various MRI systems and acquisition protocols.

In our multicenter study, ICCs for longitudinal T_2 measurements ranged from 0.73 to 0.91 with RMS-CVs (of pooled ROIs) ranging from 0.6% to 1.6%, indicating good to excellent longitudinal reproducibility. Our results indicate that T_2 mapping allows reliable evaluation of intra-subject changes in cartilage T_2 values, given that subjects are evaluated on the same scanner at each time point. These findings highlight the value of T_2 mapping as non-invasive biomarker to longitudinally assess changes in cartilage tissue composition in clinical trials, and, potentially, in future clinical practice.

Our findings compare favorably with a previous single center reproducibility study [9], using a Philips 3-Tesla scanner, reported RMS-CVs (from pooled ROIS) of 3.2% - 6.3% over a 2-month-interval. A multicenter, single vendor study by Li et al. [8], evaluated longitudinal reproducibility of cartilage T_2 values of two traveling subjects acquired at two locations with similar types of MRI scanner (GE 3T) and sequence parameters over a 10-month-interval. In the latter study, a pooled RMS-CV of 5.1% was reported, whereas ICCs were not described. Although using identical scanners and harmonized T_2 mapping protocols would be optimal from an imaging perspective, mandating uniform MRI equipment is not always feasible when performing a multicenter trial. Differences in MRI hardware and T_2 mapping sequences are often present across centers, and local requirements and restrictions (e.g. regarding acquisition time) in participating centers may prevail over optimal imaging strategies. Thus, assessing reproducibility in a multicenter multivendor setting is of key importance for future implementation of T_2 mapping in OA research, such that differences in T_2 values across centers can be taken into consideration. An overall assessment of reproducibility of cartilage T_2 measurements was provided in a multicenter multivendor by Mosher and colleagues [5]. Longitudinal cartilage T_2 measurements were evaluated by pooling 50 subjects, involving patients with OA and asymptomatic control subjects, from five centers using different MRI vendors (Philips and Siemens). A moderate to excellent reproducibility (ICC between 0.61 and 0.98) was reported over a 2-month-interval, with RMS-CVs ranging from 5% to 9% in healthy volunteers. As none of the subjects in the latter study underwent MRI scanning in more than one scanner, the within-subject reproducibility across centers could not be assessed. To our knowledge, the present work is the first study assessing the longitudinal reproducibility of cartilage T_2 mapping in a multicenter multivendor setting, using traveling human subjects.

When evaluating longitudinal reproducibility of the five participating centers, longitudinal T_2 measurements from center 1 and center 5 showed the lowest RMS-CVs and the narrowest confidence intervals. A potential explanation for this finding could be the use of fast spin echo (FSE) pulse sequences in center 1 and 5 whereas the remaining centers uses spin echo (SE) sequences [14].

Many factors can potentially cause longitudinal variation in T_2 measurements, apart from biological changes. These include environmental factors (e.g. MRI room temperature), up-

grades in MRI hardware or software, changes in phantom composition, subject features (exercise, knee flexion), and diurnal variation in T_2 measurements [8,9]. In the present study, all efforts were made to maintain conditions constant: stability in room temperatures, and no hardware or software updates during the experiment. Great care was taken to minimize and standardize physical activity level of the subjects, prior to and during scanning days. Furthermore, centers were visited in the same order at baseline and follow-up, and in each center, measurements took place at the same time of day to address potential diurnal variation in T_2 values.

We observed discrepancies in T_2 values across centers, both *in vivo* and in the phantom. These findings are in line with previous studies on multicenter comparability of cartilage T_2 measurements [9]. Several factors could potentially explain the inter-scanner differences in T_2 values we found. First, scanners from three different MRI vendors were used in this study. A multivendor comparability study by Balamoody and colleagues reported significant inter-scanner differences in cartilage T_2 values of 12 healthy subjects across three centers with different MRI vendors (GE Healthcare, Siemens and Philips). As in our study, T_2 values obtained with GE equipment were lower compared to Siemens and Philips T_2 values. A relevant potential source of variation in T_2 values from various MRI vendors are the differences in radiofrequency coil provided by each vendor [15,16], in particular the use of receive only versus transmit and receive coils. Dardzinski et al. reported higher cartilage T_2 values and lower RMS-CVs using a receive only coil compared to a transmit and receive coil [15], similar to our findings. Second, magnetic field strength among centers varied in our study, potentially influencing T_2 values [17,18]. Finally, different T_2 mapping techniques were used among centers. In center 1, a 3D FSE pulse sequence was used, whereas the remaining centers used 2D sequences. In a study by Matzat et al. [14], the influence of different T_2 mapping sequence protocols in a single scanner was assessed. In the latter study, 2D FSE resulted in 28% (SD 19%) higher T_2 values than 3D FSE. A possible explanation for this could be the stimulated echo effect in the second echo time and onwards. This might have led to artificially higher T_2 values in center 2, 3, 4 and 5, compared to the 3D sequence of center 1. Also, the application of fat saturation in T_2 mapping sequences could have been a potential source of variation in T_2 values across centers. Center 2 and center 3 used a non-fat-suppressed sequence and generated relatively low T_2 values. This is in line with a study by Ryu et al. [19], reporting that non-fat-suppressed T_2 mapping results in higher T_2 values and less reproducible T_2 measurements compared to fat-suppressed T_2 mapping. A systematic study investigating the causes of the observed differences in T_2 values across centers, with the aim of providing protocols that result in comparable T_2 values for different vendors and T_2 mapping techniques would be valuable, but this is beyond the scope of the current study. For now, we conclude that absolute T_2 values across centers should not be assumed to be comparable and should there-

fore not be pooled. In multicenter clinical trials, researchers should focus on intra-subject T_2 changes rather than absolute mean T_2 values across subject groups.

The present study has some limitations that must be noted. First, our sample size was small. We opted to perform T_2 measurements at each of the five centers in one day, hence limited sample size was feasible. Consequently, this study was statistically underpowered to report ICCs for longitudinal reproducibility of each center individually. Second, as our study was limited to healthy subjects, it is not sure whether these findings are generalizable to OA subjects.

Conclusion

In this multicenter multivendor study, *in vivo* cartilage T_2 mapping showed a good to excellent longitudinal reproducibility. Our results suggest that T_2 mapping can be used to longitudinally assess intra-subject changes in cartilage degeneration in multicenter studies, yet these findings must be interpret cautiously considering the size and nature (i.e. healthy subjects) of the sample. Given the differences in T_2 values across centers, absolute T_2 values obtained in various centers in multicenter multivendor clinical trials should not be pooled.

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Competing interest statements

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REFERENCES

1. Oei EH, van Tiel J, Robinson WH, Gold GE. Quantitative radiologic imaging techniques for articular cartilage composition: toward early diagnosis and development of disease-modifying therapeutics for osteoarthritis. Arthritis Care Res (Hoboken) 2014;66:1129-41.
2. Baum T, Joseph GB, Karampinos DC, Jungmann PM, Link TM, Bauer JS. Cartilage and meniscal T2 relaxation time as non-invasive biomarker for knee osteoarthritis and cartilage repair procedures. Osteoarthritis Cartilage 2013;21:1474-84.
3. Li X, Cheng J, Lin K, et al. Quantitative MRI using T1rho and T2 in human osteoarthritic cartilage specimens: correlation with biochemical measurements and histology. Magn Reson Imaging 2011;29:324-34.
4. Kim T, Min BH, Yoon SH, et al. An in vitro comparative study of T2 and T2* mappings of human articular cartilage at 3-Tesla MRI using histology as the standard of reference. Skeletal Radiol 2014;43:947-54.
5. Mosher TJ, Zhang Z, Reddy R, et al. Knee articular cartilage damage in osteoarthritis: analysis of MR image biomarker reproducibility in ACRIN-PA 4001 multicenter trial. Radiology 2011;258:832-42.
6. Guermazi A, Roemer FW, Burstein D, Hayashi D. Why radiography should no longer be considered a surrogate outcome measure for longitudinal assessment of cartilage in knee osteoarthritis. Arthritis Res Ther 2011;13:247.
7. Webpage: Publications & Presentations (http://www.oai.ucsf.edu/). Coordinating Center, University of California San Francisco, 2013. 2017, at http://www.oai.ucsf.edu/.)
8. Li X, Pedoia V, Kumar D, et al. Cartilage T1rho and T2 relaxation times: longitudinal reproducibility and variations using different coils, MR systems and sites. Osteoarthritis Cartilage 2015;23:2214-23.
9. Balamoody S, Williams TG, Wolstenholme C, et al. Magnetic resonance transverse relaxation time T2 of knee cartilage in osteoarthritis at 3-T: a cross-sectional multicentre, multivendor reproducibility study. Skeletal Radiol 2013;42:511-20.
10. Bron EE, van Tiel J, Smit H, et al. Image registration improves human knee cartilage T1 mapping with delayed gadolinium-enhanced MRI of cartilage (dGEMRIC). Eur Radiol 2013;23:246-52.
11. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med 2016;15:155-63.
12. Gluer CC, Blake G, Lu Y, Blunt BA, Jergas M, Genant HK. Accurate assessment of precision errors: how to measure the reproducibility of bone densitometry techniques. Osteoporos Int 1995;5:262-70.
13. Kiebzak GM, Morgan SL, Peace F. Which to use to evaluate change in BMD at follow-up: RMS-SD or RMS-%CV? J Clin Densitom 2012;15:26-31.
14. Matzat SJ, McWalter EJ, Kogan F, Chen W, Gold GE. T2 Relaxation time quantitation differs between pulse sequences in articular cartilage. J Magn Reson Imaging 2015;42:105-13.
15. Dardzinski BJ, Schneider E. Radiofrequency (RF) coil impacts the value and reproducibility of cartilage spin-spin (T2) relaxation time measurements. Osteoarthritis Cartilage 2013;21:710-20.
16. Chang G, Wiggins GC, Xia D, et al. Comparison of a 28-channel receive array coil and quadrature volume coil for morphologic imaging and T2 mapping of knee cartilage at 7T. J Magn Reson Imaging 2012;35:441-8.
17. Glaser C, Horng A, Mendlik T, et al. [T2 relaxation time in patellar cartilage--global and regional reproducibility at 1.5 tesla and 3 tesla]. Rofo 2007;179:146-52.

18. Welsch GH, Apprich S, Zbyn S, et al. Biochemical (T2, T2* and magnetisation transfer ratio) MRI of knee cartilage: feasibility at ultra-high field (7T) compared with high field (3T) strength. Eur Radiol 2011;21:1136-43.
19. Ryu YJ, Hong SH, Kim H, et al. Fat-suppressed T2 mapping of femoral cartilage in the porcine knee joint: A comparison with conventional T2 mapping. J Magn Reson Imaging 2017;45:1076-81.