Original Article

# $T_2$ mapping of healthy knee cartilage: multicenter multivendor reproducibility

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**Background:** $T_2$ mapping is increasingly used to quantify cartilage degeneration in knee osteoarthritis (OA), yet reproducibility studies in a multicenter setting are limited. The purpose of this study was to determine the longitudinal reproducibility and multicenter variation 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 with 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) as well as an average value per patient. A phantom was scanned once at each center. To evaluate longitudinal reproducibility, intraclass correlation coefficients (ICC), root-mean-square coefficient of variation (RMS-CV), and a Bland-Altman plot were used. To assess the variation of *in vivo* and phantom $T_2$ values across centers, ANOVA was performed.

**Results:** ICCs of the $T_2$ mapping measurements per ROI and the ROI's combined ranged from 0.73 to 0.91, indicating good to excellent longitudinal reproducibility. RMS-CVs ranged from 1.1% to 1.5% (per ROI) and 0.6% to 1.6% (ROIs combined) across the centers. A Bland-Altman plot did not reveal a systematic error. Evident, but consistent, discrepancies in $T_2$ values were observed across centers, both *in vivo* and in the phantom.

**Conclusions:** The results of this study suggest 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.

**Keywords:** Knee; cartilage; magnetic resonance imaging (MRI); $T_2$ mapping; reproducibility

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## 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 with 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 $T_2$ mapping reproducibility and the variation of $T_2$ relaxation times among various MRI systems with different field strengths and acquisition protocols.

## Methods

### *Study design*

Five medical centers located in different geographical parts of The Netherlands participated in this prospective observational study. In these centers, a multicenter randomized controlled trial (RCT) is currently conducted on the outcomes of conservative versus operative treatment of a traumatic meniscal tear (trial number NTR 4511). $T_2$ mapping is used as an outcome measure for deterioration of knee cartilage two years after a meniscal tear in this study. 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 6 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 the variation of $T_2$ values across centers, cross-validation was performed in the human subjects as well as a phantom. Approval from the Institutional Review Board of our institution (MEC 2014-096) 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 to assess the variation of the $T_2$ 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).

### *Data acquisition*

MRI acquisition parameters are summarized per center 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

 

**Table 1** MRI sequence parameters

| 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 × PE) | 288×192 | 192×144 | 256×256 | 256×190 | 300×247 |
| 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) | 1,263 | 2,000 | 2,690 | 2,170 | 3,582 |
| 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 |

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.

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 MathWorks, 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 (JV) 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*) as scans will be analyzed in the same manner in the aforementioned RCT on the outcomes traumatic meniscal tear treatment. 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). Besides $T_2$ values per ROI, an average $T_2$ value per patient was calculated to assess the variation of $T_2$ relaxation times across centers. The automated registration of the follow-up $T_2$ mapping scan to the high-resolution scan 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.

### *Statistical analyses*

The longitudinal reproducibility of $T_2$ measurements in each cartilage ROI and the ROIs combined was evaluated

 

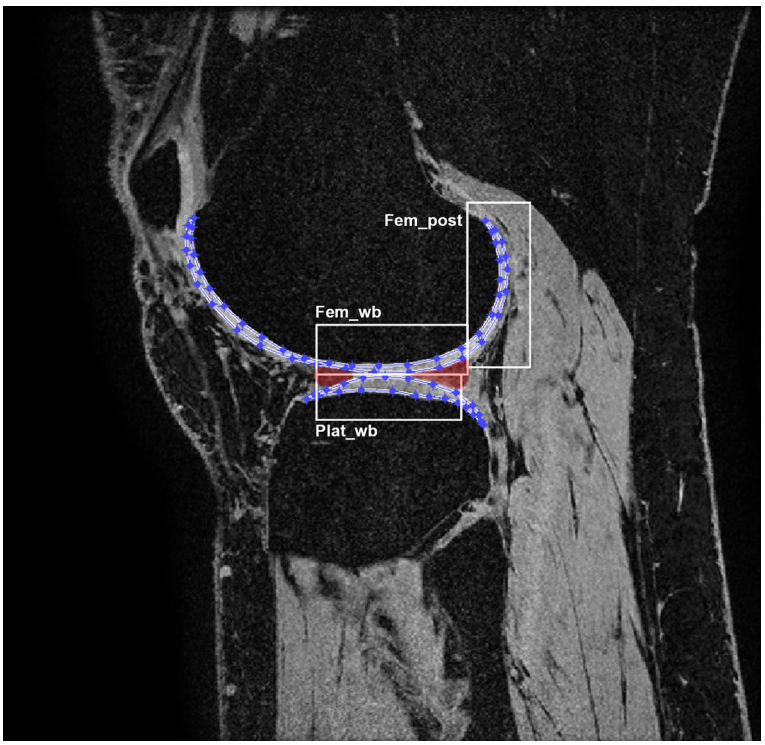


**Figure 1** Cartilage segmentation on sagittal high-resolution FSPGR image, lateral compartment. Blue dotted lines surround the segmented mask; white boxes represent the ROIs. Fem_post, posterior femoral condyle; Fem_wb, weight-bearing femoral condyle; Plat_wb, weight-bearing tibial plateau.

with intraclass correlation coefficients (ICCs) for absolute agreement of single measures, using a two-way random model. As there were not enough subjects to calculate an ICC per center, we pooled 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). To assess the reproducibility per center, we calculated coefficients of variation (CVs, defined as the standard deviation (SD) normalized by the mean value of the measurements) of the differences in $T_2$ measurements between both measurements 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 Glüer *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. A Bland-Altman plot was made per ROI 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.

To assess the variation of $T_2$ relaxation times across centers, we compared the $T_2$ relaxation times of the subjects (average $T_2$ value per subject) of the baseline measurements and the phantom between centers. Variation in $T_2$ values was analyzed using one-way ANOVA with Dunn's Multiple Comparison Test. Data was tested for normality using Shapiro-Wilk tests. 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 T2 measurements*

The ICCs of the $T_2$ measurements pooled across all centers

 

**Table 2** Agreement of longitudinal *in vivo* $T_2$ measurements per cartilage ROI

| Region of interest | ICC | | RMS-CV | | | | |
|---|---|---|---|---|---|---|---|
| | ICC | CI-95 | Center 1 | Center 2 | Center 3 | Center 4 | Center 5 |
| Femoral cartilage | | | | | | | |
| Weight-bearing | | | | | | | |
| Medial | 0.91 | 0.78–0.96 | 1.6 | 3.4 | 5.2 | 1.2 | 0.9 |
| Lateral | 0.82 | 0.59–0.92 | 3.3 | 2.2 | 3.3 | 4.2 | 1.3 |
| Posterior | | | | | | | |
| Medial | 0.91 | 0.80–0.97 | 1.5 | 4.0 | 2.3 | 1.2 | 2.0 |
| Lateral | 0.85 | 0.66–0.94 | 1.1 | 6.2 | 2.4 | 2.9 | 1.1 |
| Tibial cartilage | | | | | | | |
| Medial | 0.86 | 0.69–0.94 | 2.7 | 1.8 | 4.0 | 4.5 | 1.4 |
| Lateral | 0.73 | 0.44–0.89 | 2.8 | 1.2 | 2.7 | 6.2 | 1.1 |
| Overall (ROIs combined) | 0.90 | 0.86–0.93 | 1.1 | 1.3 | 1.4 | 1.6 | 0.6 |

Data of the human subjects was pooled. For the ICC, data of all centers was pooled. RMS-CV shows the precision of agreement for longitudinal $T_2$ measurements in human subjects, shown as percentage. The lower the RMS-CV, the higher the precision. ROI, region of interest; ICC, intraclass correlation coefficient; CI-95, 95% confidence interval; RMS-CV, root mean square coefficient of variation.

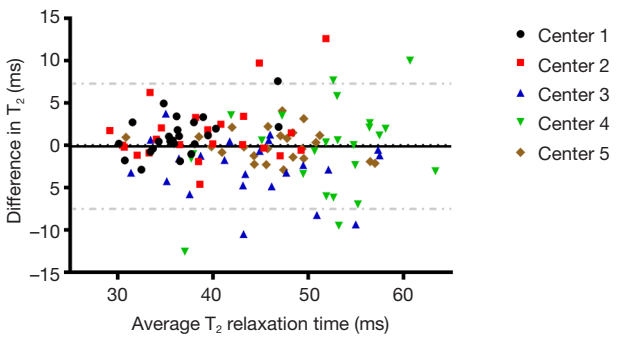


**Figure 2** Bland-Altman plot showing the differences in *in vivo* $T_2$ values between baseline and follow-up against the mean $T_2$ values plotted per cartilage ROI for each subject. Each colored shape represents the four subjects with each six ROIs. The bold line represents the mean difference, dotted lines represent the limits of agreement.

ranged from 0.73 to 0.91 for the different ROIs, indicating a good to excellent reproducibility (*Table 2*). When using the average $T_2$ values per subject, we found an excellent reproducibility with an ICC of 0.90. In the same table, the RMS-CVs of the longitudinal $T_2$ measurements per center are presented for the different ROIs and the ROIs combined. The overall (average $T_2$ value per subject) RMS-CV in each center ranged from 0.6% to 1.6%. The Bland-Altman plot revealed a mean difference of −0.11 milliseconds between baseline and follow-up $T_2$ measurements (*Figure 2*). Lowest mean differences were observed in center 1 and center 5, indicating highest reproducibility. A systematic error was not observed.

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 milliseconds). 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 variation of in vivo and phantom $T_2$ measurements*

In *Figure 3A*, the average $T_2$ values per subject are plotted for each center, showing discrepancies across centers. A statistically significant difference in $T_2$ 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. Moreover, phantom $T_2$ measurements

 

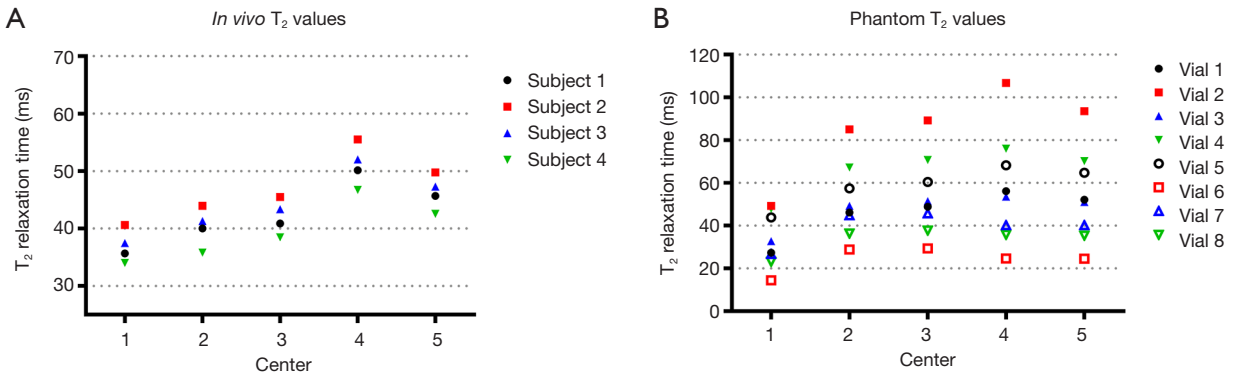


**Figure 3** Average $T_2$ values of subjects and phantom vials per center. (A) Baseline average $T_2$ values per subject in each center; (B) Phantom $T_2$ values plotted per vial in each center. The concentration of manganese chloride for each vial was: vial 1 =0%, vial 2 =5%, vial 3 =10%, vial 4 =15%, vial 5 =20%, vial 6 =30%, vial 7 =50%, and vial 8 =80%.

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 3B*). Phantom stability was verified [ICC 0.90, 95% CI (0.856–0.928) over a 6-month-interval].

## 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 variation of $T_2$ measurements in different cartilage ROIs in a multicenter setting, using various MRI systems and acquisition protocols. ICCs for longitudinal $T_2$ measurements ranged from 0.73 to 0.91 with RMS-CVs 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 are consistent with a previous single center reproducibility study (9), using a 3 Tesla scanner, reporting RMS-CVs of 3.2% to 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 and sequence parameters over a 10-month-interval. In the latter study, a 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 two different MRI vendors. 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 lowest mean differences. 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), upgrades 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 variation 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 therefore 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 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 only a limited sample size was feasible. Consequently, this study was statistically underpowered to report ICCs for longitudinal reproducibility of each center individually. With a larger sample size it might have been possible to find reference $T_2$ values of healthy cartilage for each scanner (brand and field strength), which was beyond the scope of the current study. Second, as our study was limited to healthy subjects, it is not sure whether these findings are generalizable to OA subjects and care should be taken to use this information in other contexts such as cartilage repair.

## Conclusions

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 interpreted with caution considering the size and nature (i.e., healthy subjects) of the study population. Given the variation 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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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/qims-20-674). EHGO serves as an unpaid editorial board member of *Quantitative Imaging in Medicine and Surgery*. The authors have no other conflicts of interest to declare.

*Ethical Statement:* This study was approved by the Institutional Review Board of our institution (MEC 2014-096) and written consent of all subjects was obtained.



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