

A comparison of multi-echo spin-echo and triple-echo steady-state T₂ mapping for in vivo evaluation of articular cartilage

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Received: 17 April 2015 / Revised: 6 August 2015 / Accepted: 10 August 2015 / Published online: 3 September 2015
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Abstract

Objectives To assess the clinical relevance of T₂ relaxation times, measured by 3D triple-echo steady-state (3D-TESS), in knee articular cartilage compared to conventional multi-echo spin-echo T₂-mapping.

Methods Thirteen volunteers and ten patients with focal cartilage lesions were included in this prospective study. All subjects underwent 3-Tesla MRI consisting of a multi-echo multi-slice spin-echo sequence (CPMG) as a reference method for T₂ mapping, and 3D TESS with the same geometry settings, but variable acquisition times: standard (TESSs 4:35min) and quick (TESSq 2:05min). T₂ values were compared in six different regions in the femoral and tibial cartilage using a Wilcoxon signed ranks test and the Pearson correlation coefficient (r). The local ethics committee approved this study, and all participants gave written informed consent.

Results The mean quantitative T₂ values measured by CPMG (mean: 46±9ms) in volunteers were significantly higher compared to those measured with TESS (mean: 31±5ms) in all

regions. Both methods performed similarly in patients, but CPMG provided a slightly higher difference between lesions and native cartilage (CPMG: 90ms→61ms [31%], p=0.0125; TESS 32ms→24ms [24%], p=0.0839).

Conclusions 3D-TESS provides results similar to those of a conventional multi-echo spin-echo sequence with many benefits, such as shortening of total acquisition time and insensitivity to B₁ and B₀ changes.

Key points

- 3D-TESS T₂ mapping provides clinically comparable results to CPMG in shorter scan-time.
- Clinical and investigational studies may benefit from high temporal resolution of 3D-TESS.
- 3D-TESS T₂ values are able to differentiate between healthy and damaged cartilage.

Keywords T₂ mapping · Cartilage · CPMG · TESS · Osteoarthritis

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Abbreviations

TESS Triple-echo steady state sequence
CPMG Carr-Purcell-Meiboom-Gill sequence

Introduction

Transverse relaxation time (T₂) mapping in articular cartilage has been previously reported as a reliable marker for the evaluation of collagen matrix and water content. The changes in T₂ values have been demonstrated to correlate with alterations in water content, as well as collagen structure and organization, and are linked to changes in hyaline cartilage and its depletion [1–3]. To date, T₂ mapping of cartilage has been successfully used

in many applications related to biomechanical and biochemical analysis of cartilage tissue [4–17]. Although the loss of glycosaminoglycans is an early sign of osteoarthritis (OA) and collagen depletion occurs in later stages, the potential of T_2 as a marker for the grading of cartilage degeneration in OA has also been demonstrated [18].

T_2 maps are typically calculated from a series of T_2 -weighted images acquired with different echo times. However, the accuracy and reliability of the resulting T_2 maps is highly dependent on the method used to record the initial T_2 -weighted images.

A multi-spin-echo pulse sequence [e.g., Carr-Purcell-Meiboom-Gill (CPMG) [19]] is a widely used method for in vivo T_2 mapping. This sequence acquires signals from multiple time points along the T_2 decay for each k-space line during a single repetition time. However, this is accompanied by the consequent signal contamination by stimulated echoes [20]. Acquiring the complete T_2 decay curve is also time-consuming and frequently requires segmented imaging strategies.

Another possibility for acquiring T_2 -weighted images is a single-spin-echo strategy. It is well known that maps generated with a series of single-echo spin-echo (SE) images suffer from steady state effects (i.e., different T_1 weightings) in the images. To prevent this, long transverse relaxation (TR) times are necessary, which may limit clinical applications. In addition, the total scan time is substantially longer compared to CPMG because the sequence must be repeated for each echo time separately [21].

Recently, a triple-echo steady-state (TESS) relaxometry method was introduced for fast and accurate T_2 and T_1 mapping [22, 23]. This sequence has several advantages over conventional T_2 mapping: it is very fast, the data are acquired in a single scan, and the quantification of T_2 is markedly insensitive to B_1 . To date, the clinical performance of 3D-TESS for T_2 mapping in cartilage has not yet been evaluated.

Therefore, the purpose of this study was to assess the clinical relevance of T_2 relaxation times, measured by three-dimensional (3D) triple-echo steady-state (3D-TESS), in knee articular cartilage compared to conventional multi-echo spin-echo T_2 -mapping.

Materials and methods

Patients

The right knees of 10 patients (35.1 ± 10.5 years) with a focal cartilage lesion and 13 age-matched volunteers (31.4 ± 9.4 years) were measured in this prospective study. The local

ethics committee approved this study, and all participants gave written, informed consent. Inclusion criteria for volunteers were: no signs of any cartilage lesion in the knee joint on standard morphological magnetic resonance (MR) sequences; and no meniscal and ligament damage. In patients, only subjects with focal lesions in the femoral cartilage were included. Three patients underwent surgical procedures on the femoral cartilage (matrix-associated chondrocyte transplantation [MACT], Pridie drilling, and mosaicplasty), and the remaining patients were diagnosed with chondropathy grade 2 to 4 according to the International Cartilage Repair Society (ICRS) classification.

MR examinations

All subjects underwent MR examinations of the knee joint on a 3 Tesla Tim TRIO MR scanner (Siemens HealthCare, Erlangen, Germany). An eight-channel knee coil (Siemens HealthCare, Erlangen, Germany) was used for all MR scans. The examination consisted of two methods: a multi-echo multi-slice spin echo sequence (CPMG) as a reference method for T_2 mapping; and a 3D-TESS with the exact same geometry settings as in the CPMG sequence but with two modifications, a standard (TESSs, acquisition time 4:35 min) and a quick (TESSq, acquisition time 2:05 min) sequence. For TESSq, the total acquisition time was reduced by using a phase-and-slice partial Fourier acquisition. The abbreviation TESS refers to TESSs throughout the entire manuscript. With TESS imaging, the three steady-state free precession signal amplitudes (F_1 , F_0 , and F_{-1}) were acquired within separate radiofrequency cycles (each signal within one at the same echo time) to enable a shorter repetition time and mitigate possible susceptibility effects [22]. CPMG T_2 maps were calculated using the Syngo console tool Mapit (Siemens, Erlangen, Germany), and, for 3D-TESS, the scripting framework IceLuva was used [24]. To ensure the possibility of evaluating all T_2 maps at once by copying regions-of-interest (ROIs), the frequency calibration was double-checked before each scanning to avoid chemical shift artefacts. The summary of all sequence parameters is in the Table 1.

MR data evaluation

T_2 values were compared in six different regions in the femoral (anterior AFC, mid MFC, posterior PFC) and tibial (anterior ATC, mid MTC, posterior PTC) cartilage (Fig. 1). Each ROI was further subdivided into equally thick superficial and deep layers. The ROIs were selected in the JiveX DICOM Viewer (JiveX 4.3; VISUS Technology Transfer GmbH, Bochum, Germany) by a

Table 1 Sequence parameters used for CPMG T₂ mapping and novel 3D-TESS T₂ mapping

Sequence parameter	CPMG	3D-TESSs	3D-TESSq
Slice thickness	3 mm	3 mm	3 mm
Slice spacing	3 mm	3 mm	3 mm
Repetition time	2060 ms	1114 ms	1114 ms
Echo time	[11.9, 23.8, 35.7, 47.6, 59.5, 71.4, 83.3, 95.2] ms	5.06	5.06
Averages	1	1	1
Frequency sampling	100 %	100 %	100 %
Phase sampling	100 %	100 %	100 %
Phase partial Fourier	no	no	6/8
Slice partial Fourier	no	no	7/8
Acquisition matrix	320 × 320	320 × 320	320 × 320
Field-of-view	160 × 160	160 × 160	160 × 160
Flip angle	180°	15°	15°
Total acquisition time	4:30 min	4:36 min	2:05 min
Pixel bandwidth	161 Hz/pixel	446 Hz/pixel	446 Hz/pixel

radiologist (N.N.) with 16 years of experience. To assess inter-observer variability, another two observers (N.N. 10 years of experience, N.N., 15 years of

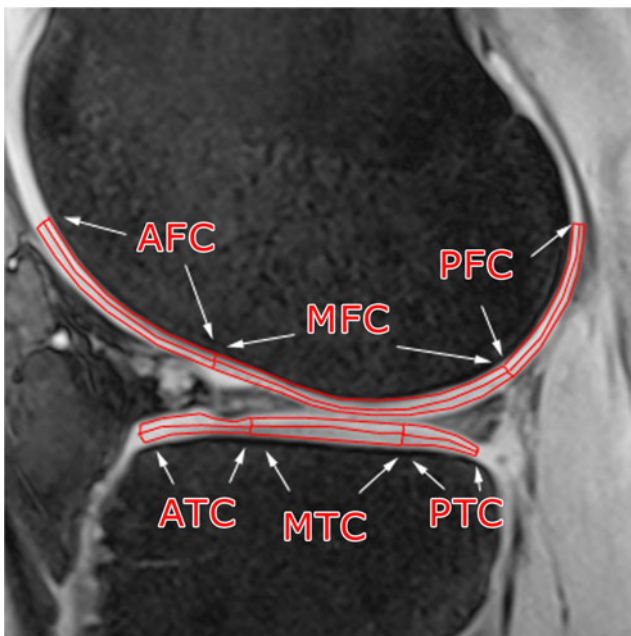


Fig. 1 ROI selection on 3D-TESS image (the second acquired MR image, referred to as F₀). AFC: anterior femoral cartilage, MFC: mid femoral cartilage, PFC: posterior femoral cartilage, ATC: anterior tibial cartilage, MTC: mid tibial cartilage, and PTC: posterior tibial cartilage

experience), blinded to previous results, evaluated five volunteers and five patients, and the coefficient of variation was calculated.

Statistical analysis

The difference between absolute T₂ values calculated with different mapping techniques (CPMG versus 3D-TESS and 3D-TESSq versus 3D-TESSs) was expressed as a *P*-value calculated by a Wilcoxon signed ranks test. Pearson correlation coefficients were calculated, and standard deviations (SDs) of the ROIs were compared. Both absolute values and percentage differences between CPMG and 3D-TESS were evaluated. In patients, the T₂ values from focal chondral lesions were compared to the adjacent native cartilage and the ability to differentiate between healthy and depleted cartilage was assessed. All statistical calculations were performed in SPSS version 19.0 (SPSS Inc., Chicago, IL) and a *P*-value less than 0.05 was considered statistically significant.

Results

The subjects had the following demographic characteristics: volunteers (5 males, mean age 28.8 ± 5.8 years, mean BMI 23.8 ± 3.7; 8 females, mean age 33.1 ± 11.1 years, mean BMI 22.8 ± 2.9), patients (8 males, mean age 36.8 ± 11 years, mean BMI 24.7 ± 2.6; 2 females mean age 28.1 ± 4.7 years, mean BMI 22.9 ± 4.8). Both techniques provided artefact-free T₂ maps (Figs. 2, 3 and 4). The T₂ values measured with 3D-TESS were systematically lower than those measured with CPMG. When all cartilaginous regions were pooled, the average T₂ values were 52 ± 10 ms (CPMG) and 29 ± 5 ms (3D-TESS). For individual cartilage layers separately, the mean T₂ values in the superficial layer were 59 ± 7 ms (CPMG) and 33 ± 2 ms (TESS), and in the deep layer, 46 ± 9 ms (CPMG) and 27 ± 5 ms (TESS). In general, the difference between 3D-TESS and CPMG T₂ values was statistically significant in all regions. The T₂ values measured by CPMG showed a high correlation with T₂ values calculated from 3D-TESS, primarily in the weight-bearing zones of the tibia and femur, and the other zones correlated only moderately (Tables 2 and 3).

The SDs for TESS-T₂ were slightly lower than for CPMG-T₂; however, this difference was not statistically significant (28 ± 6 % and 30 ± 12 %, *P* = 0.579). When comparing cartilage layers, the SD did not demonstrate any significant differences between the superficial (TESS 26 ± 8 %, CPMG 32 ± 10 %) and the deep zone (TESS 29 ± 7 %, CPMG 29 ± 8 %).

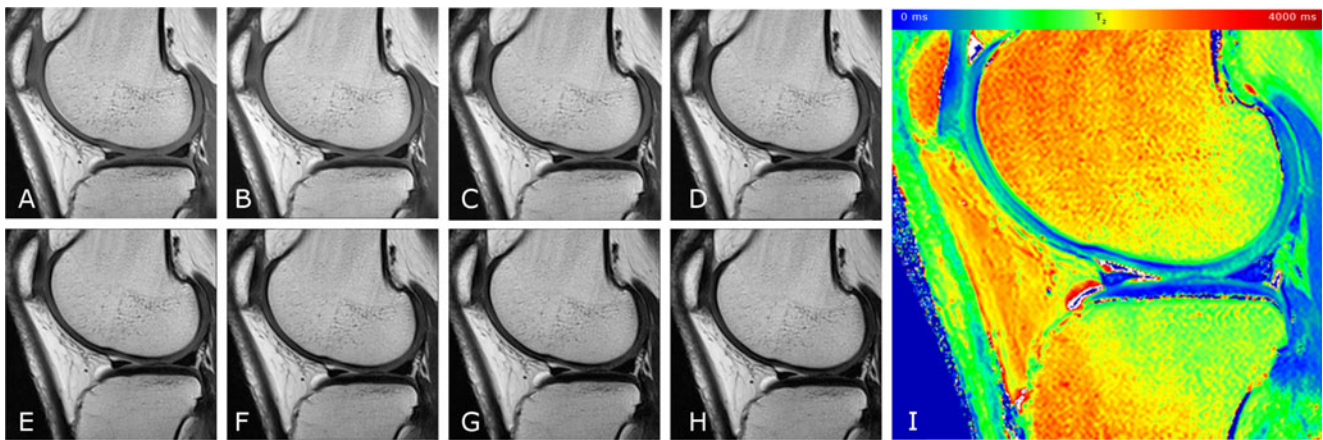


Fig. 2 The series of MR images acquired with different TEs used for the T_2 map generation with the CPMG technique. A: TE = 11.9 ms, B: TE = 23.8 ms, C: TE = 35.7 ms, D: TE = 47.6 ms, E: TE = 59.5 ms, F: TE =

71.4 ms, G: TE = 83.3 ms, H: TE = 95.2 ms, and I: resulting pseudo-colour-coded T_2 map

Both T_2 mapping techniques were able to detect the changes between chondral lesions and native cartilage. For CPMG, the mean T_2 in cartilaginous lesions was 90 ± 50 and in native cartilage, it was 62 ± 25 ms. For 3D-TESS, the mean T_2 in cartilaginous lesions was 32 ± 6 , and in native cartilage, it was 24 ± 8 ms. Example T_2 maps of native and damaged cartilage are depicted in Fig. 5.

The comparison between TESSq and TESSs showed almost no difference between T_2 values. On average, $T_2(3D\text{-TESS}q)$ was 31 ± 2 ms and $T_2(3D\text{-TESS}s)$ was 31 ± 3 ms. The mean Pearson correlation coefficient calculated from the whole cartilage in volunteers and patients was 0.816, ranging from 0.750 to 0.911 in different cartilage regions. The example of correlation in the femoral and tibial cartilage is depicted in Fig. 6.

The mean coefficient of variation between different observers was 6.4 % (femoral cartilage, $T_2(\text{CPMG})$), 8.1 % (tibial cartilage, $T_2(\text{CPMG})$), 5.8 % (femoral cartilage, $T_2(3D\text{-TESS})$) and 10.8 % (tibial cartilage, $T_2(3D\text{-TESS})$).

Discussion

The results of our study indicate that T_2 relaxation times in the cartilage of the knee joint, calculated from a novel 3D-TESS sequence, are highly consistent with those calculated by a classic CPMG sequence. Although the absolute T_2 values were significantly lower for 3D-TESS, this decrease was systematic, and the T_2 values were highly correlated between 3D-TESS and CPMG in most of the selected regions. In Ref. [23], the authors demonstrated that TESS-based T_2 quantification provides accurate T_2 values in excellent agreement with single-echo spin echo reference measurements, while CPMG resulted in a substantial overestimation of T_2 due to stimulated echo contributions. The observed significant difference between TESS- T_2 and CPMG- T_2 may, thus, be mainly attributed to stimulated echo contamination present in the CPMG scans. In addition, the increase of T_2 values in the region affected by the magic angle effect (posterior femoral condyle in our case) was observable with both techniques. According to

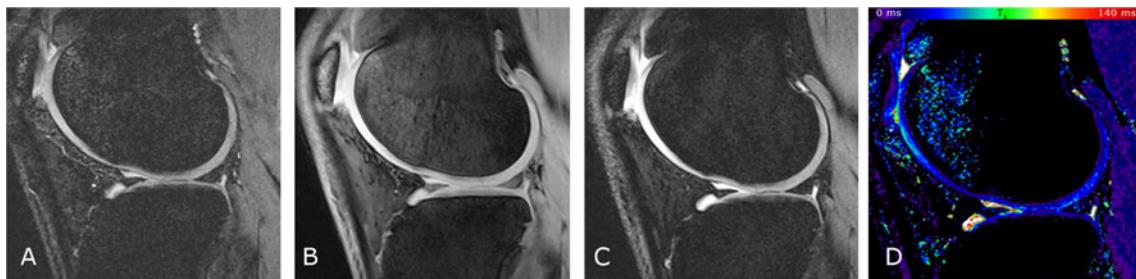


Fig. 3 MR images of different contrasts acquired using 3D-TESS. A, B, and C: the three base steady-state signal modes (A: F_1 , B: F_0 , C: F_{-1}), and D: resulting pseudo-colour coded T_2 map

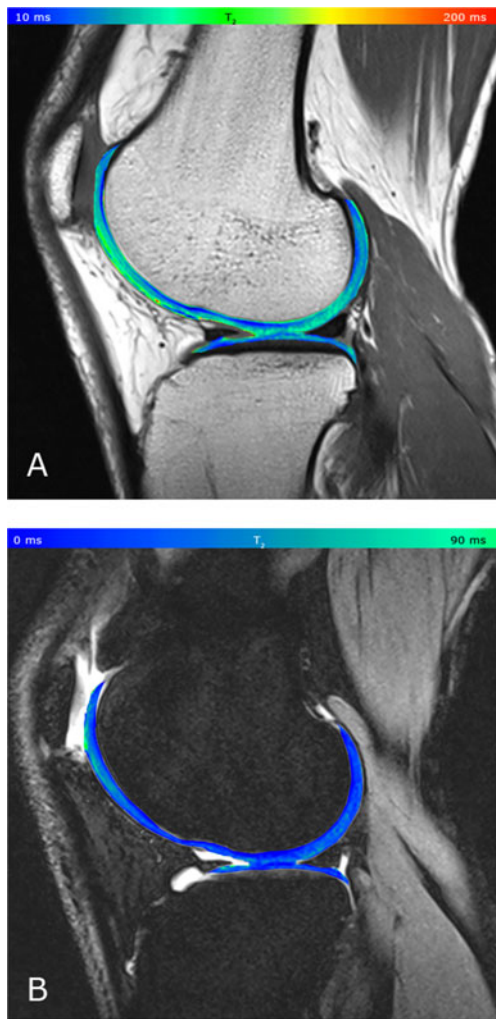


Fig. 4 A: T₂ map acquired by CPMG, pseudo-colour-coded and overlaid on a morphological T₂-weighted image from a 32-year-old healthy volunteer (TE=11.9 ms); B: T₂ map acquired by 3D-TESS, pseudo-colour-coded and overlaid on the second acquired MR image (F₀). The typical zonal stratification in cartilage is observable with both techniques. However, T₂(CPMG) provides apparently higher dynamic contrast of T₂ values with better depiction of cartilaginous layers

Mosher et al., the greatest variation in cartilage T₂ with regard to the magic angle effect is observed in the superficial 20 % of cartilage [25]. This is in concordance

with the presented results, although we divided the cartilage into two layers rather than three because of limited in vivo resolution.

The great advantage of 3D-TESS for cartilage T₂ mapping is the decrease of total scan time. At our institute, the routine (CPMG) T₂ mapping at 3T requires four and a half minutes. In our study, for comparison purposes, we primarily used a total-acquisition-time-matched version of 3D-TESS. However, we were able to decrease the acquisition time of 3D-TESS down to 2:05 min by using a phase-and-slice partial Fourier sampling, keeping the resulting cartilage T₂ values without a statistically significant change, compared to the total-acquisition-time-matched version of 3D-TESS. This feature would be extremely beneficial in studies where a higher temporal resolution is desired. A typical example would be the physiological analysis of cartilage changes during in vivo loading.

For instance, Nishii et al. used CPMG T₂ mapping in their in vivo loading study with a 13-minute long CPMG sequence version [26]. Marnett et al. evaluated the unloading effect on articular cartilage prior to and during the MR scan with a 4:09-minute long CPMG-based sequence [27]. In another study, the changes in cartilage water content in cartilage under compression were detected using T₂ mapping, with an acquisition time of 7:30 minutes [28]. The limitation with all such experiments is that the decrease of T₂ values during the MR experiment under loading cannot be excluded with certainty. Therefore, there is a need to shorten the acquisition time of T₂ experiments to a minimum. In this case, 3D-TESS seems to be the ideal T₂ mapping technique for such investigational applications. However, fast T₂ mapping with 3D-TESS could also be beneficial for routine clinical applications, providing increased patient comfort and reducing costs.

We also hypothesized that the SD of T₂ from ROIs selected on cartilage would be lower with 3D-TESS due to its more robust T₂ calculation. The results, however, showed the SDs were the same, no matter which technique was

Table 2 Femoral Cartilage

	AFCs	AFCd	d/s [%]	MFCs	MFCd	d/s [%]	PFCs	PFCd	d/s [%]
T ₂ (CPMG) (ms)	62.4	53.40	14.4	68.93	55.42	19.6	59.36	54.29	8.5
T ₂ (TESS) (ms)	37.0	28.32	23.4	32.69	23.10	29.3	34.53	29.59	14.3
P-value (Wilcoxon)	0.002	0.002		0.002	0.002		0.002	0.002	
Pearson coefficient	0.535	0.455		0.701	0.808		0.497	0.300	

CPMG multi-echo multi-slice spin echo sequence; TESS triple echo steady state; AFCs anterior femoral condyle, superficial zone; AFCd anterior femoral condyle, deep zone; MFCs medial femoral condyle, superficial zone; MFCd medial femoral condyle, deep zone; PFCs posterior femoral condyle, superficial zone; PFCd posterior femoral condyle, deep zone; d/s deep/superficial ratio

Table 3 Tibial Cartilage

	ATCs	ATCd	d/s [%]	MTCs	MTCd	d/s [%]	PTCs	PTCd	d/s [%]
T ₂ (CPMG) [ms]	51.17	33.58	34.4	52.65	38.00	27.8	57.65	42.78	25.8
T ₂ (TESS) [ms]	32.08	20.40	36.4	30.39	23.78	21.8	31.18	24.73	20.8
P-value (Wilcoxon)	0.003	0.002		0.002	0.002		0.002	0.002	
PEARSON COEFFICIENT	0.136	0.806		0.807	0.865		0.740	0.913	

CPMG multi-echo multi-slice spin echo sequence; TESS triple echo steady state; ATCs anterior tibial condyle, superficial zone; ATCd anterior tibial condyle, deep zone; MTCs tibial femoral condyle, superficial zone; MTCd medial tibial condyle, deep zone; PTCs posterior tibial condyle, superficial zone; PTCd posterior tibial condyle, deep zone; d/s deep/superficial ratio

used. Moreover, SDs calculated in our study were consistent with those published in other studies; e.g., Nieminen et al. found an SD of T₂ in bovine cartilage ranging from 12.5 to 29 % [29], and Kurkijärvi et al., as well as Juras et al., observed an SD of T₂ in human cadaver samples between 13.3 - 41.5 % [30] and 23 - 34 %, respectively [31]. Since all of these studies were performed in vitro, it can be assumed that motion artefacts did not contribute to those high SDs. High SDs of T₂ in cartilage tissue could be attributed to relatively large tissue anisotropy and heterogeneity due to collagen fibre organization [32].

It has been previously demonstrated that focal cartilage lesions, as well as the cartilage repair tissue, are characterized by T₂ elevation [14, 33–35]. This focal T₂ increase was attributed either to collagen disorganization or to cartilage swelling, accompanied by water volume increase. Similarly, in our study, we observed an increase in T₂ differences between native cartilage and lesions. For CPMG, this difference was slightly larger (32 %) compared to 3D-TESS (24 %). Since both differences were statistically significant, the clinical relevance of both techniques is comparable.

Our study has some limitations. Our patient group was relatively small and the diagnoses were inconsistent. It would be necessary to validate these findings in a larger patient group with the same type of cartilage lesions or repair tissues. Moreover, the lesions selected in our study were quite severe, resulting in relatively large T₂ value changes. It would be interesting, however, to investigate the sensitivity of 3D-TESS to subtle T₂ changes, where 3D-TESS would be expected to perform better as it provides more accurate T₂ values. This is primarily because 3D-TESS is less prone to errors, while CPMG substantially overestimates T₂ due to stimulated echo contributions.

3D-TESS is insensitive to B₀ and B₁ heterogeneities and may, thus, provide more accurate T₂ values with lower SDs. Moreover, the three-dimensional nature of 3D-TESS allows reformatting of T₂ maps in arbitrary planes, expanding the usefulness of this sequence to other tissues (e.g., ligaments, menisci) or more challenging joints for MR imaging (MRI; e.g., hip, shoulder, temporo-mandibular). The 3D-TESS

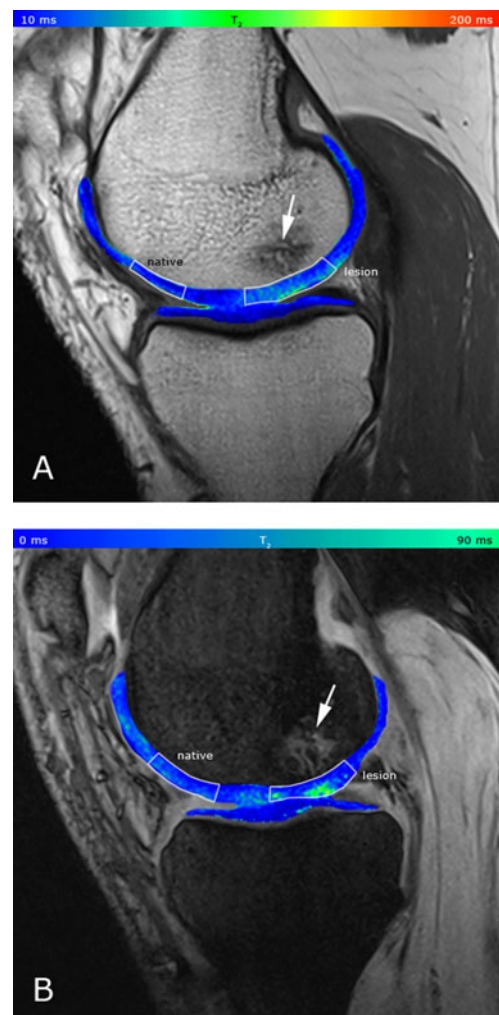
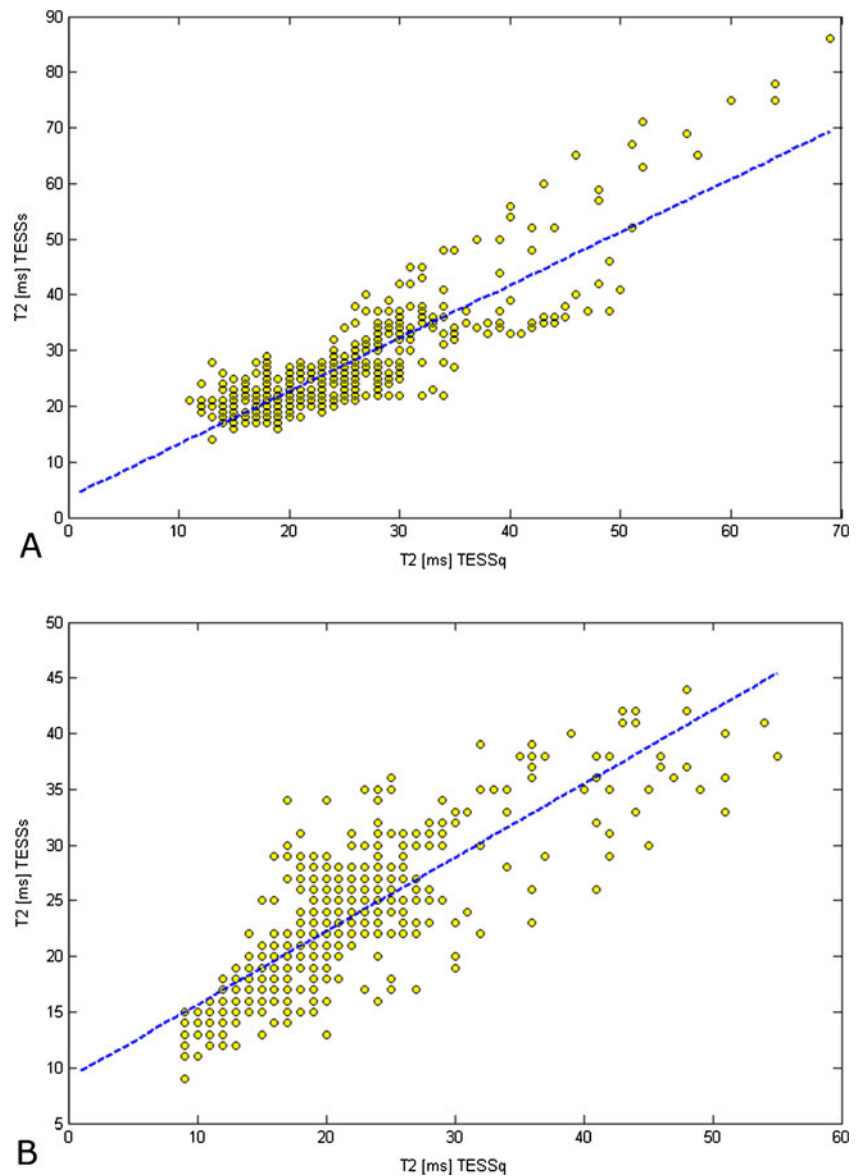


Fig. 5 A: T₂ map acquired by CPMG, pseudo-colour-coded and overlaid on a morphological image of a 41-year-old patient with Pridie drilling on the medial femoral condyle (TE=11.9 ms); the ratio of native and lesion cartilage T₂s is 0.81. B: T₂ map acquired by 3D-TESS, pseudo-colour-coded and overlaid on the second acquired MR image (F₀); the ratio of native and lesion cartilage T₂s is 0.83. Focal increase in T₂ values is observable with both techniques ('lesion'). Bone oedema is also present (large arrow). The dynamic range of the CPMG T₂ map is higher compared to the 3D-TESS T₂ map, therefore, the lesion appears to be more diffuse, although the ratios of native and lesion cartilage T₂s are comparable between CPMG and 3D-TESS

Fig. 6 A: The correlation of the individual T_2 values of an example ROI from the femoral cartilage acquired by TESSq and TESSs ($r=0.893$, $N=433$). B: The correlation of the individual T_2 values of this example ROI from the tibial cartilage acquired by TESSq and TESSs ($r=0.862$, $N=544$)



sequence also produces T_1 maps (not tested in this study) that may have great clinical potential, but require additional B_1 mapping scans.

Conclusion

The results of this study demonstrate the clinical utility of a 3D-TESS sequence for T_2 mapping of human knee cartilage. 3D-TESS provides results similar to those of a conventional multi-echo spin-echo sequence with many benefits, such as shortening of total acquisition time and insensitivity to B_1 and B_0 changes. T_2 mapping with 3D-TESS was able to differentiate between healthy and

damaged cartilage tissue, indicating its great potential for clinical studies.

Acknowledgments The scientific guarantor of this publication is Prof. Siegfried Trattnig, MD. The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article. This study has received funding by the Austrian Science Fund (FWF) P 25246 B24 and Slovak Grant Agency APVV-0431-12. One of the authors has significant statistical expertise. Institutional review board approval was obtained. Written informed consent was obtained from all subjects (patients) in this study. Methodology: prospective, cross sectional study, performed at one institution.

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