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T2 and T2* mapping in patients after matrix-associated autologous chondrocyte transplantation: initial results on clinical use with 3.0-Tesla MRI

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Abstract *Objectives:* To use T2 and T2* mapping in patients after matrix-associated autologous chondrocyte transplantation (MACT) of the knee, and to compare and correlate both methodologies. *Methods:* 3.0-Tesla MRI was performed on 30 patients (34.6±9.9 years) with a follow-up period of 28.1±18.8 months after MACT. Multi-echo, spin-echo-based T2 mapping using six echoes and gradient-echo-based T2* mapping using six echoes were prepared. T2 and T2* maps were obtained using a pixel-wise, mono-exponential, non-negative least-squares fit analysis. Region-of-interest analysis was performed for mean (full-thickness) as well as deep and superficial aspects of the cartilage repair tissue and control cartilage sites. *Results:* Mean T2 values (ms) were comparable for the control cartilage (53.4±11.7) and the repair tissue (55.5±11.6) ($p>0.05$). Mean T2* values (ms) for control cartilage (30.9±6.6) were significantly higher than those of the repair tissue (24.5±8.1) ($p<0.001$). Zonal stratification was more pronounced for T2* than for T2. The correlation between T2 and T2* was highly significant ($p<0.001$), with a Pearson coefficient between 0.276 and 0.433. *Conclusion:* T2 and T2* relaxation time measurements in the evaluation of cartilage repair tissue and its zonal variation show promising results, although the properties visualised by T2 and T2* may differ.

Keywords T2 · T2* · MRI · 3.0 Tesla · Cartilage repair

Introduction

The ability of magnetic resonance imaging (MRI) to visualise morphological and biochemical changes in articular cartilage could enable the use of MRI for follow-up of different therapy procedures [1, 2]. Since single cartilage injuries can also lead to overall osteoarthritis, even in young patients, and thus can significantly reduce the quality of life, therapy is of great importance. Surgical cartilage repair procedures of these single, full-thickness cartilage defects produce cartilage repair tissue and thus altered cartilage in addition to the relatively healthy adjacent cartilage. The overall goal of cartilage repair tissue, especially after cost- and time-intensive cartilage transplantation techniques, is to produce a repair tissue that has the same constitution and the same functional and mechanical properties as hyaline cartilage [3].

Assessment of these properties non-invasively during the follow-up after cartilage repair requires modern evaluation techniques, one of which is biochemical MRI [4–9]. The MRI techniques most often reported to possibly visualise cartilage structure and composition are delayed

gadolinium-enhanced MRI of cartilage (dGEMRIC) and quantitative T2 mapping [10–14]. In addition to those techniques, various other promising methodologies are available in biochemical cartilage imaging. T1rho, diffusion-weighted imaging (DWI), chemical-exchange-dependent saturation transfer (CEST), or magnetisation transfer (MT) contrasts are all able to add some additional information about the ultrastructure of articular cartilage [9, 15–17]. In this regard, T2* mapping can also be seen as a useful addition with which to visualise the constitution of articular cartilage and cartilage repair tissue [18–22].

For T2 relaxation, which reflects the interaction of water and the extracellular matrix, particularly collagen content and tissue anisotropy, a zonal assessment from the subchondral border to the joint surface is desirable [23]. At ultra-high fields, this zonal pattern could also be evaluated for T2* relaxation [21]. In animal examinations and, recently, in initial in vivo studies, zonal T2 evaluation was able to characterise the constitution and possibly the maturation of cartilage repair tissue [24–26].

The goal of the present initial study was to assess and correlate zonal T2 and T2* relaxation times in a patient cohort after matrix-associated autologous cartilage transplantation (MACT). In this cross-sectional evaluation, a further aim was to compare the two methodologies in their visualisation of control cartilage and cartilage repair tissue over time.

Materials and methods

Patient population

In this cross-sectional evaluation, 30 patients with a follow-up period of 28.1±18.8 months after matrix-associated autologous chondrocyte transplantation (MACT) (11 female, 19 male; mean age 34.6±9.9 years; age range 20–56 years) were included. MR measurements were performed during standard follow-up patient care at postoperative intervals of 3, 6, 12, 24, 36/42 and 60 months. MACT is a sophisticated two-step surgical approach for the treatment of middle to large full-thickness cartilage defects. The defects were located on the femoral condyle (six lateral, 24 medial), with a mean size of 3.87 cm^2 (range 2.3–9.7 cm^2). For MACT, Hyalograft®C, a hyaluronan-based scaffold (Fidia Advanced Biopolymers, Abano Terme, Italy), was used. To control for other variables that might affect outcome and as the MACT procedure was performed for single cartilage defects in stable and otherwise healthy knees, patients with other knee pathologies (e.g. instability, ligament or meniscal tears, fractures, malalignment) were excluded from the study. MACT was performed for all patients by the same two senior orthopaedic/trauma surgeons with an identical surgical technique; furthermore an identical modern rehabilitation protocol was performed in every patient. Ethical approval for this study was given by our university ethics commission, and written informed consent was obtained from all patients before enrolment in the study.

Image acquisition

MR imaging was performed on 3-Tesla MRI system (Magnetom Trio, Siemens Medical Solutions, Erlangen, Germany), with a gradient strength of 40 mT/m, using a dedicated eight-channel knee coil (Invivo, Gainesville, FL, USA). All patients were positioned consistently, with the joint space in the middle of the coil and the knee extended in the coil. Patients underwent imaging after at least 0.5 h of rest to avoid changes in T2 or T2* relaxation because of different loading before MR measurement [27].

The protocol for all MR measurements was identical and consisted of a multi-echo, spin-echo (SE) sequence using six echoes for the standard T2 mapping, a gradient-echo (GRE) sequence using six echoes for assessment of the T2* maps, and a morphological proton-density turbo-spin-echo sequence (PD-TSE), as well as a morphological 3D true–fast imaging with steady-state precession (True-FISP) sequence. T2 relaxation times were obtained from T2 maps reconstructed using sagittal SE acquisition, with a repetition time (TR) of 1,200 ms and six echo times (TE) of 13.8 ms, 27.6 ms, 41.4 ms, 55.2 ms, 69 ms and 82.8 ms. Field of view (FoV) was 160×160 mm, pixel matrix 384×384 and voxel size 0.4×0.4×3.0 mm. The bandwith was 228 Hz/pixel, with 12 slices, and total acquisition time was 4 min 9 s. T2* maps were constructed using a GRE acquisition with a TR of 600 ms and a TE of 5.7 ms, 9.8 ms, 14 ms, 18.1 ms, 22.2 ms and 26.4 ms. FoV, matrix, slice thickness and voxel size were kept consistent for the T2 and the T2* sequences to guarantee the same in-plane and out-of-plane resolution for better comparability. The bandwith was 260 Hz/pixel, with 12 slices, and the total acquisition time was 2 min 4 s. The morphological PD-TSE sequence was obtained with a TR of 2,400 ms, a TE of 38 ms and a flip angle of 160°. FoV was 120×120 mm, the pixel matrix was 512×512 and the voxel size was 0.2×0.2×2 mm. The bandwidth was 244 Hz/pixel, and total imaging time for 24 slices was 6:11 minutes. The 3D-True-FISP sequence was performed with a TR of 8.9ms and a TE of 3.8ms. The FoV was 160×160 mm, the pixel matrix was 384×384 and the voxel size was 0.4×0.4×0.4 mm. The bandwidth was 200 Hz/pixel, and the data acquisition time for this sequence was 6 min 47 s for 320 slides. After loading the isotropic 3D-True-FISP data set into the built-in 3D viewing tool, the sagittal T2 and T2* acquisitions, as well as the high-resolution morphological PD-TSE sequence, were planned to cover the cartilage repair area on the femoral condyle to obtain biochemical and high-resolution morphological information about the cartilage repair tissue and the adjacent cartilage.

Data analysis

T2 and T2* maps were obtained using a pixel-wise, mono-exponential, non-negative least-squares (NNLS) fit analysis. In combination with the morphological images provided by the PD-TSE and the 3D-True-FISP sequences and the surgical reports, the cartilage repair tissue was identified on the T2 and T2* map images. Regions of interests (ROI) were manually drawn by an experienced senior musculoskeletal radiologist, in consensus with an orthopaedic surgeon with a special interest in musculoskeletal MR imaging. The ROIs that covered the full thickness of cartilage repair tissue were positioned in the identified cartilage repair area. A region of morphologically normal-appearing cartilage was selected as a reference (control) cartilage. Control cartilage was defined as normal on the morphological PD-TSE and True-FISP sequences if cartilage thickness was preserved, the surface was intact and no intrachondral signal alterations were visible. As all cartilage repair areas were located within the weight-bearing zone of one femoral condyle, ROIs of healthy-appearing cartilage could also be placed within the weight-bearing zone. Two ROIs were selected within the cartilage repair tissue covering the whole cartilage transplant, and two ROIs, of a size approximately equal to that of the cartilage repair tissue, were selected within the healthy control cartilage. In addition, the full thickness of cartilage repair tissue, as well as the control cartilage, was divided into equal-sized deep and superficial aspects. Examples of T2 and T2* maps with corresponding PD-TSE images are provided in Figs. 1 and 2. Analysis was performed on two consecutive slides covering the cartilage repair tissue. Thus, in every patient, eight ROIs for healthy control cartilage and eight ROIs for cartilage repair tissue were analysed. The analysis was performed on the T2 maps and the ROIs were subsequently copied and, if necessary, movement-corrected on the T2* map. Altogether, 480 T2 ROIs were assessed, as well as 480 T2* ROIs. The mean number of pixels for each of the different zones was 236±114.

In addition to the evaluation of all patients combined, the cross-sectional patient cohort was divided in terms of follow-up into a short-term, mid-term and long-term follow-up period, with ten patients in each group. The postoperative follow-up periods were 7.5±4.1 months (ranging from 3 to 12 months) for the short-term follow-up, 26.4±5.0 months (ranging from 24 to 36 months) for the mid-term follow-up and 50.6±8.2 months (ranging from 42 to 60 months) for the long-term follow-up. The mean age at the time point of MRI within the different follow-up intervals also increased. At the short-term follow-up, the mean age of patients was 31.4±11.0 years; at the mid-term follow-up 33.8±8.1 years; and at the long-term follow-up MRI examination 38.5±10.1 years.

Statistical evaluation was performed for the mean T2 and T2* values to provide a statement about the relaxation times of the mean (full thickness) of articular cartilage and cartilage repair tissue. This also enabled the deep and superficial aspects to be evaluated with a focus on the stratification of T2 and T2* relaxation. Quantitative evaluation was done by analyses of variance using a three-way ANOVA with random factors, considering the different measurements within each patient. For the trend in between the cartilage layers, a three-way analysis of variance, with random effects and two repeated measure

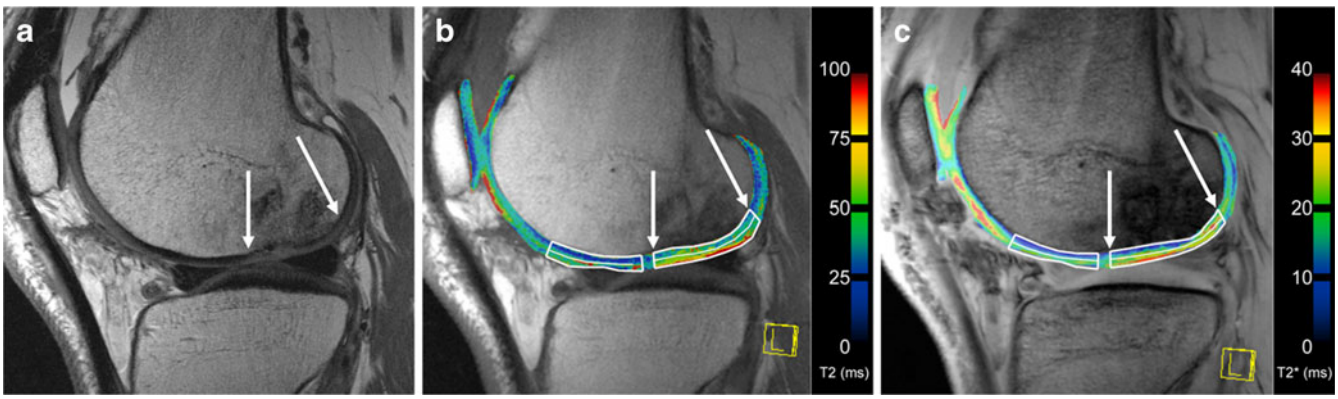

Fig. 1 Depiction of cartilage in a patient 6 months after MACT of the lateral femoral condyle. Morphological PD-TSE sequence (**a**), matched quantitative T2 (**b**), and T2* (**c**) maps. *Arrows* mark the area of cartilage repair. ROIs, considering a possible zonal variation, provide information on the mean (full-thickness) as well as the deep and superficial aspect of control cartilage (*left*) and cartilage repair tissue (*right*, *arrows*). Zonal stratification is visible for both T2 and T2* images in most parts of the cartilage. A possible "magic angle" effect is visible within the trochlea. Higher T2/T2* values are apparent in the cartilage repair tissue, compared with the adjacent cartilage

factors, was performed. For correlation between T2 and T2* values, a correlation using the Pearson coefficient was achieved. The SPSS version 16.0 software (SPSS Institute, Chicago, IL, USA) for Mac (Apple, Cupertino, CA, USA) was used, and a *P* value less than 0.05 was considered statistically significant.

Results

T2 relaxation

T2 values are given in milliseconds (ms). Mean (full-thickness) T2 values for healthy control cartilage for all patients together were 53.4±11.7; zonal T2 values showed a highly significant increase from deep (51.5±10.3) to superficial zones (55.3±9.5) ($p<0.001$). T2 values for the cartilage repair tissue after MACT showed mean (full-thickness) relaxation times of 55.5±11.6 with a significant increase from deep (53.9±11.3) to superficial zones (57.0±12.9) ($p=0.035$) There was no significant difference in the mean (full-thickness) T2 values ($p=0.118$) or the T2 values for the deep ($p=0.067$) or superficial ($p=0.239$) cartilage aspects between healthy control cartilage and cartilage repair tissue.

The cross-sectional evaluation over time showed a slight increase for the healthy control cartilage, with mean (full-thickness) T2 values of 50.5±9.5 for the short-term, 53.7±8.8 for the mid-term and 56.0±55.8 for the long-term follow-up. This increase over time was not significant between short-term and mid-term ($p=0.107$), or between mid-term and long-term ($p=0.220$); however, the increase was significant between short-term and long-term follow-up ($p=0.006$). The mean (full-thickness) T2 values of the cartilage repair tissue, however, showed a clearly significant decrease from short-term (59.9±11.5) to mid-term (51.1±10.1) follow-up ($p<0.001$) and a slight and non-significant increase from mid-term to long-term (55.4±11.8) follow-up ($p=0.069$). The difference between the short-term and long-term follow-up was also not significant ($p=0.084$).

When comparing control cartilage and cartilage repair tissue at the different follow-up intervals, mean (full-thickness) T2 values of cartilage repair tissue were significantly higher than those of control cartilage ($p<0.001$) at the short-term follow-up, whereas at the mid-term ($p=0.207$) and long-term ($p=0.800$) follow-up, no significant differences between cartilage repair tissue and control cartilage could be assessed. Table 1 and Fig. 3 depict the zonal T2 values for the different follow-up intervals.

T2* relaxation

T2* values are given in milliseconds (ms). All patients together showed a mean (full-thickness) T2* value for healthy control cartilage of 30.9±6.6; with regard to zonal assessment, a significant increase could be described from deep (27.9±7.2) to superficial (33.9±6.9) cartilage aspects. The cartilage repair tissue after MACT showed a mean (full-thickness) T2* value of 24.5±8.1 and a significant increase from deep (21.6±7.3) to superficial (27.5±9.4) aspects for zonal T2* values ($p<0.001$). When comparing T2* values of the healthy control cartilage with those of the cartilage repair tissue, the T2* values for mean (full-thickness) as well as for

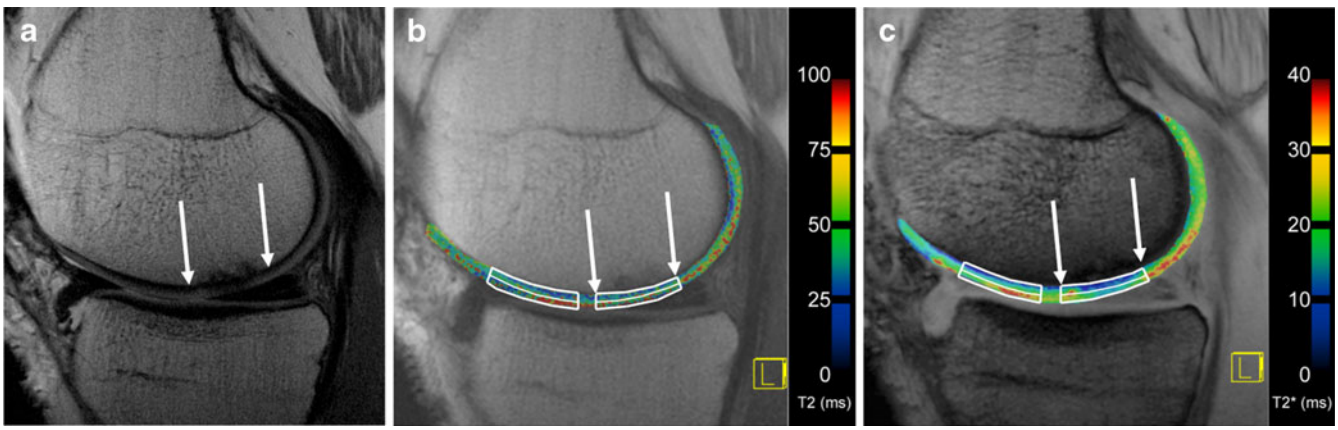

Fig. 2 Results of MRI in a patient 60 months after MACT of the medial femoral condyle. Morphological PD-TSE sequence (**a**), matched quantitative T2 (**b**), and T2* (**c**) maps. *Arrows* mark the area of cartilage repair. ROIs, considering a possible zonal variation, provide information on the mean (full-thickness) as well as the deep and superficial aspects of control cartilage (*left*) and cartilage repair tissue (*right*, *arrows*). Zonal stratification is visible for both T2 and T2* images in most parts of the cartilage. A possible "magic angle" effect occurs within the posterior femoral condyle. Lower T2* values and similar T2 values within the cartilage repair tissue are apparent, compared with the adjacent cartilage

deep and superficial cartilage aspects were significantly lower in the cartilage repair tissue ($p<0.001$).

With regard to the different postoperative intervals, the T2* values demonstrated stability over time. Mean (full-thickness) T2* values were 31.4±6.2 for the short-term interval, 31.0±6.7 for the mid-term interval and 30.4±7.0 for the long-term interval, with no significant difference among the groups (short-term to mid-term, $p=0.749$; mid-term to long-term, $p=0.697$; short-term to long-term, $p=0.472$). The cartilage repair tissue, on the other hand, showed significantly higher T2* values at the short-term follow-up (31.0±8.1) than at the mid-term follow-up (20.7±6.1) ($p<0.001$), and stable values between the mid-term and long-term (22.2±6.0) follow-up ($p=0.232$). The difference between the short-term and long-term follow-up was also significant ($p<0.001$).

The comparison of mean (full-thickness) T2* values for healthy control cartilage and cartilage repair tissue at the different postoperative follow-up time points revealed comparable values at the short-term follow-up (0.793). For the mid-term ($p<0.001$) and long-term ($p<0.001$) postoperative intervals, however, significantly lower mean (full-thickness) T2* values were found in cartilage repair tissue than in healthy control cartilage.

Table 1 and Fig. 3 visualise the zonal T2* values for the different follow-up intervals.

Correlation between T2 and T2*

The correlation between T2 and T2* values was assessed for the deep cartilage areas, the superficial cartilage areas and the mean (full-thickness) cartilage area. As demonstrated by Fig. 4, significant correlations could be assessed with Pearson correlation coefficients of 0.276 ($p<0.001$) for the deep cartilage aspects, 0.433 ($p<0.001$) for the superficial cartilage aspects and 0.348 ($p<0.001$) for the mean values.

Discussion

The present study demonstrates that, using both T2 and T2*, the mean (full-thickness) and zonal analysis of healthy articular cartilage and cartilage repair tissue is possible. The evaluation of the mean values, representing the full thickness of cartilage, reveals comparable values for cartilage repair tissue and healthy control cartilage when looking at T2 relaxation times; whereas T2* relaxation times show lower mean values in cartilage repair tissue than in control cartilage. As articular cartilage is stratified, primarily according to the orientation of collagen within a three-dimensional network [28, 29], its ultrastructure should be reported based on a zonal evaluation. This zonal evaluation, performed in the present study, shows a clear increase in T2, as well as T2* values, from the subchondral border to the joint surface for healthy control cartilage and also for the cartilage repair tissue. The role of this stratification in T2 values in healthy articular cartilage of the knee joint has been widely reported [14, 23, 30]. The basis of this stratification may become more obvious when considering in vitro studies on articular cartilage, which suggest that the appearance is strongly influenced by the anisotropic arrangement of the collagen

Table 1 Zonal (deep and superficial) T2 and T2* values (ms) for the different follow-up intervals after MACT of the femoral condyle

			Deep	Superficial	*P* value
Short-term	Control cartilage	T2	47.7±9.5*	53.5±11.0	<0.001
		T2*	28.0±6.8	34.8±6.7	<0.001
	Repair tissue	T2	58.3±10.6	61.4±13.2	0.0045
		T2*	28.0±7.2	34.0±9.7	<0.001
Mid-term	Control cartilage	T2	51.9±10.4	55.5±8.5	0.001
		T2*	28.0±7.3**	33.9±7.0**	<0.001
	Repair tissue	T2	50.2±10.3	52.1±11.1	0.067
		T2*	17.9±5.6**	23.5±7.2**	<0.001
Long-term	Control cartilage	T2	54.2±9.8	57.8±9.4	<0.001
		T2*	27.5±4.6***	33.3±7.3***	<0.001
	Repair tissue	T2	53.4±11.6	57.5±12.7	<0.001
		T2*	19.2±4.6***	25.3±7.8***	<0.001

Short term follow-up period ranged from 3 to 12 months, mid-term follow-up ranged from 24 to 36 months, long-term follow-up ranged from 42 to 60 months. *P* value is given for the trend in increasing T2 and T2* relaxation times from subchondrial to superficial
*Significant difference between control cartilage and cartilage repair tissue (deep, $p<0.001$; superficial, $p=0.002$)
**Significant difference between control cartilage and cartilage repair tissue (deep, $p<0.001$; superficial, $p<0.001$)
***Significant difference between control cartilage and cartilage repair tissue (deep, $p<0.001$; superficial, $p<0.001$)
All other T2 and T2* values showed no significant difference between control cartilage and cartilage repair tissue ($p>0.05$)

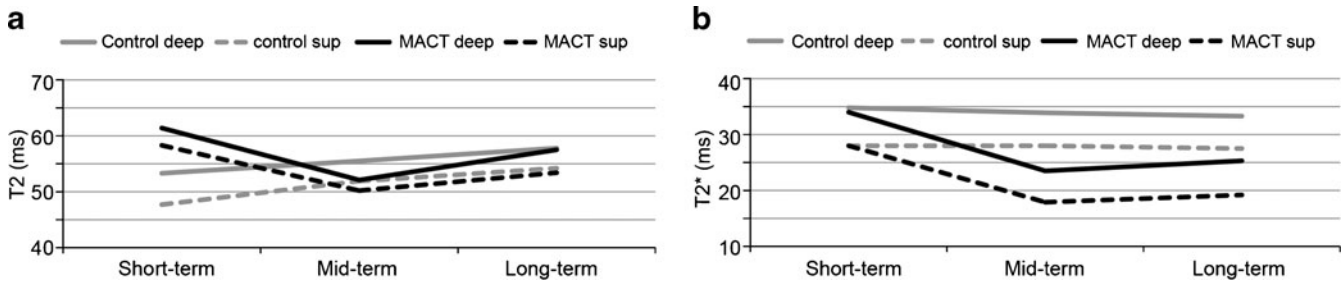

Fig. 3 The zonal pattern of T2 (**a**) and T2* (**b**) values (ms), at the different follow-up intervals after MACT, is visualised. The cross-sectional assessment is classified into a short term (3–12 months), a mid-term (24–36 months) and a long-term (42–60 months) follow-up period. Compared with the deep zone (*dotted lines*), higher T2 as well as T2* values could be assessed in the superficial zone (*continuous line*) for the control cartilage, and also for the cartilage repair tissue. The difference between the deep and the superficial aspects, however, appears clearer for T2* relaxation. Whereas T2 values for healthy control cartilage and cartilage repair tissue adapt over time; for T2*, the opposite is true, and clearly lower values can be demonstrated for the cartilage repair tissue at the longer follow-up interval

fibres and by their orientation to the main magnetic field [13, 28, 31]. Moreover, an animal study on cartilage repair procedures in horses [26] showed that a zonal increase from deep to superficial cartilage aspects can be correlated to the hyaline-like structure of the cartilage repair tissue. The results for the T2 relaxation times of cartilage repair tissue in the present study are comparable to those of Welsch et al. [25], where patients were evaluated after a similar cartilage repair procedure. When the different postoperative intervals are examined, the stratification of the T2 values is enhanced. The increase in T2 values from deep to superficial zones was slightly significant at the short-term follow-up, slightly non-significant at the mid-term follow-up and clearly significant at the long-term follow-up. These findings were in accordance with an in vitro study by Watrin-Pinzano et al. [24], where an increase in the stratification of the T2 measurements was seen to reflect the maturation of cartilage repair tissue. The zonal increase in T2* values from deep to superficial cartilage layers was very obvious for all the different postoperative intervals. These results suggest that T2* might, at a certain point, also be able to visualise the collagenous architecture of articular cartilage. Nevertheless, because the proteoglycan concentration is also known to be different in deep and superficial cartilage [32], the zonal dependence of T2* values may not only be caused by the collagenous architecture, but also might be attributable to differences in all macromolecules and their orientation.

Considering the correlation between the T2 and the T2* measurements, a clearly significant association between the two relaxation times is notable. The Pearson correlation coefficients, however, revealed relatively low values, especially for the evaluation of the deep cartilage layer. The lower correlation within the deep cartilage zone might also be due to the influence of local susceptibility fields on T2*. These local fields can operate at the macroscopic level, i.e. at the bone–cartilage interface, or at the microscopic level, i.e. associated with the underlying microstructure of the cartilage. If these processes produce local changes in the macroscopic static field gradients, these might be more distinct in the deep cartilage zone. This problem in the evaluation of the cartilage near the

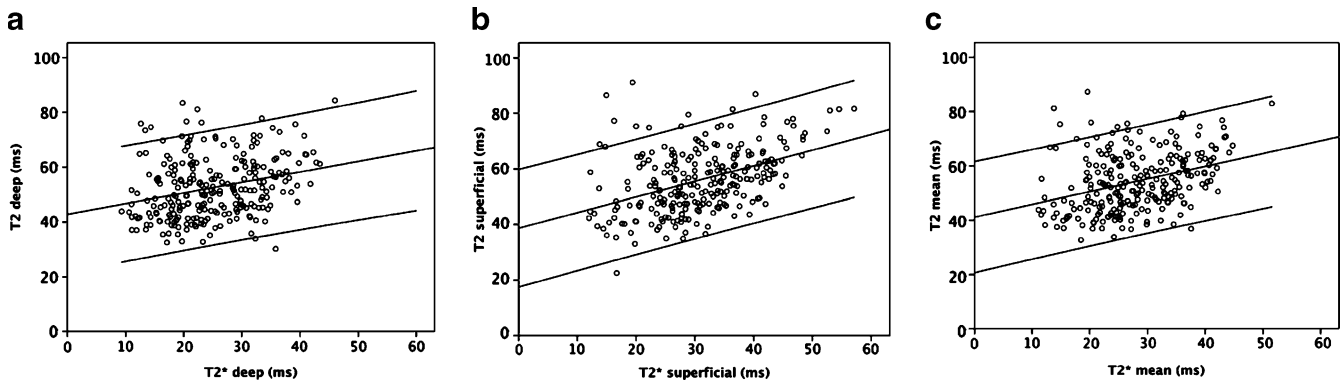

Fig. 4 Correlation plots, with 95% confidence interval, of the T2 and T2* analysis. The assessment of the deep (**a**), the superficial (**b**) and the mean (full-thickness) (**c**) aspects of articular cartilage are visualised. The correlation for the superficial cartilage aspects seems a little stronger than that for the deep aspect

subchondral bone plate might also account for the differences in the zonal stratification between T2 and T2*, with a clearer increase from deep to superficial relaxation times in T2* than in T2.

When considering the differences between the control cartilage according to the different postoperative intervals, interestingly, the T2 values of the healthy control cartilage show an increase from short-term to mid-term and from mid-term to long-term, whereas the T2* values remained unchanged. An increase in T2 values is reported inconsistently in literature [1]; however, most studies report an increase in T2 values because of age or degeneration [33–35]. The increase in T2 values of healthy cartilage, reported in the present study, might be due to the more advanced age of our cohort, or to early degenerative changes in the group with the long-term follow-up after cartilage repair. In the ultrastructure of cartilage, the reason for this increase is either an enhanced water concentration, or a change within the collagenous matrix [1, 14, 35]. T2* values, on the other hand, showed no increase over time in the healthy control cartilage sites, which might be due to a lower sensitivity to hydration. However, this remains unclear as histological validation is lacking.

The cartilage repair tissue shows a decrease in T2, as well as T2* values, over time. This decrease occurs between the short-term follow-up (6–12 months) and the mid-term follow-up (24–26 months). When comparing the mid-term and the long-term (42–60 months) follow-up, T2 and T2* relaxation times remain stable. It has been reported that the decrease in T2 values in cartilage repair tissue over time reflects cartilage repair tissue maturation [36]. This possible effect of maturation can thus be found with T2 and T2* relaxation.

Possibly more important than the evaluation of the repair tissue over time is the comparison between the cartilage repair tissue and its internal, healthy control cartilage. Visualised in Fig. 3, for T2 relaxation, higher T2 values of cartilage repair tissue in the short-term follow-up adapt to those of healthy control cartilage over time. For T2* relaxation, comparable values in the cartilage repair tissue and control cartilage at the short-term interval diverge over time, with lower values for the repair tissue in the mid-term and long-term follow-up. Assuming that T2 relaxation demonstrates hydration, as well as the collagen orientation and concentration, the reported T2 values might imply that the cartilage repair tissue, at the mid- and long-term follow-up, shows an organisation comparable to that of the control cartilage in terms of hydration and collagenous architecture. The significantly lower T2* values in the cartilage repair tissue, compared with the control cartilage, at the mid- and long-term follow-up, might again be proof that T2* does not measure the same properties of cartilage as T2. Even in the longer follow-up after autologous cartilage transplantation procedures, histological evaluations have reported repair tissue as hyaline-like or as a mixture of hyaline-like tissue and fibrocartilage [37–40], and hence the ultrastructure of the cartilage repair tissue is not completely comparable to that of healthy cartilage. This fact might be better visualised by T2* relaxation. Considering that MR studies about the use of dGEMRIC in patients after cartilage repair report a reduced glycosaminoglycan concentration in the long-term follow-up after cartilage repair [6, 41], it could be the case that T2* visualises different properties of articular cartilage in addition to collagen, also including, perhaps, proteoglycan aggregates. Thus, T2* relaxation might be a sensitive tool in addition to T2 relaxation in describing the ultrastructure of articular cartilage. Problematic for both methodologies might be the fact that T2 or T2* values can increase or decrease when the structure of cartilage changes from healthy to abnormal or when differences between control cartilage and cartilage repair tissue are reported. This is discussed for T2 in a review article by Burstein et al. [1] and might be a limitation of T2* as well.

The lack of histological proof for the results of the present study may be the clearest limitation of the present study, especially in the assessment of T2* relaxation, where few studies about articular cartilage are available. However, as MRI has replaced arthroscopic biopsies in the postoperative evaluation of cartilage repair, histological samples were not available. Nevertheless, future in vitro or animal studies are required to clarify the role of T2* in the assessment of cartilage ultrastructure. The next limitation, the mentioned sensitivity of the T2* sequence to susceptibility artefacts, also has to be reviewed in future studies and in vitro models. In particular, the zonal assessment of T2* might be limited because of the accumulation of artefacts especially in the deep zone, near to the subchondral bone plate. Hence the clear stratification of T2* values measured in cartilage repair tissue might be due to postoperative surgically induced artefacts caused by metal abrasion or blood. Another limitation is the cross-sectional nature of this study, as well as the relatively low number of patients within the three different follow-up groups. When considering the present results, a comparison of T2* with other biochemical MR techniques would be desirable. Furthermore, the dependency of T2* on the "magic angle" effect must be resolved in future methodical evaluations of articular cartilage.

The original goal, to implement T2* as fast T2 mapping, providing comparable information of the cartilage ultrastructure with the additional benefit of three-dimensional acquisition, high signal, high spatial resolution and short imaging time, could not be reached sufficiently. In studies on preparing a significant imaging time reduction for dGEMRIC, using a gradient-echo approach instead of the standard inversion recovery sequence [6, 41, 42], comparably high correlations could not be reached when comparing T2* with the standard multi-echo, spin-echo T2 approach.

In conclusion, this initial study reveals that both zonal T2 mapping and T2* mapping, at 3.0-Tesla MRI, in a

clinical setup, are promising tools in the assessment of cartilage ultrastructure in the follow-up after cartilage repair. The properties of articular cartilage and cartilage repair tissue, visualised by T2*, are related, but not similar to the properties demonstrated by T2.

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