Association between quantitative MRI and ICRS arthroscopic grading of articular cartilage

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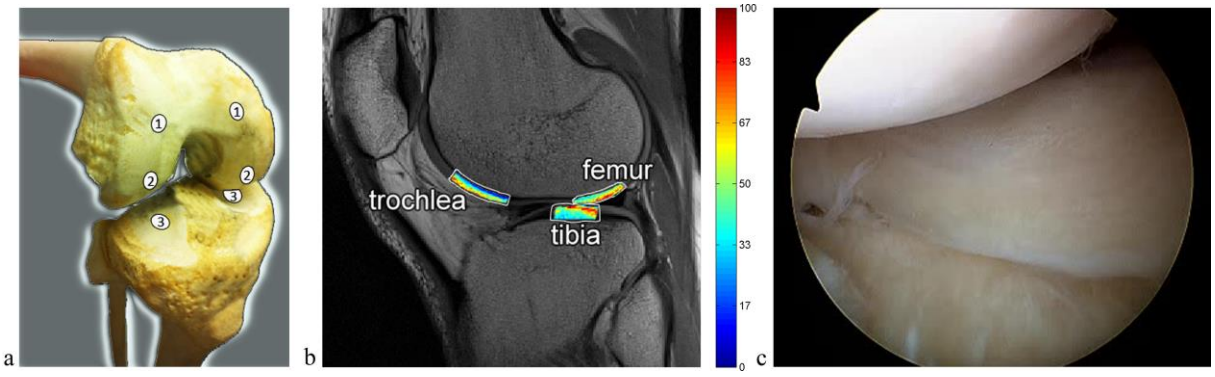

Abstract

Purpose. To investigate the association of quantitative MRI (qMRI) parameters with arthroscopic grading of cartilage degeneration. Arthroscopy of the knee is considered to be the gold standard of OA diagnostics, however, it is operator-dependent and limited to the evaluation of the articular surface. qMRI provides information on the quality of articular cartilage and its changes even at early stages of a disease.

Methods. qMRI techniques included T_1 relaxation time, T_2 relaxation time and dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) mapping at 3 Tesla in 10 patients. Due to a lack of generally accepted semi-quantitative scoring systems for evaluating severity of cartilage degeneration during arthroscopy, the International Cartilage Repair Society (ICRS) classification system was used to grade the severity of cartilage lesions. qMRI parameters were statistically compared to arthroscopic grading conducted with the ICRS classification system.

Results. qMRI parameters were not linearly related to arthroscopic grading. Spearman correlation coefficients between qMRI and arthroscopic grading were not significant. The relative differences in qMRI parameters of superficial and deep cartilage varied with degeneration, suggesting different macromolecular alterations in different cartilage zones.

Conclusions. Results suggest that loss of cartilage and the quality of remaining tissue in the lesion site may not be directly associated with each other. The severity of cartilage degeneration may not be revealed solely by diagnostic arthroscopy and thus qMRI can have a role in the investigation of cartilage degeneration.

Keywords: Articular cartilage, Osteoarthritis, MRI, Arthroscopy

Introduction

In osteoarthritis (OA), articular cartilage (AC) is progressively damaged, characterized by collagen network degradation, loss of proteoglycans, and increase in water content [10]. Current treatments of OA are unable to adequately recover degenerated AC, Consequently, a diagnosis at early stage of the disease, when cartilage is not yet compromised, may provide the most effective chances to stop AC degeneration or even reverse the process and to target any preventive treatment cost-effectively.

Traditional diagnostic methods for OA, such as radiography and arthroscopy, have been considered through the years to be the most accurate investigation techniques. Radiography, however, is unable to directly visualize articular cartilage and surrounding soft tissue structures to reveal early changes in tissue quality. Arthroscopic assessment consists of visual and manual investigation and can be considered to be the gold standard for OA diagnosis [3, 17]. It can reveal macroscopic features of early stages of OA including the loss of tissue integrity at articular surface and tissue softening. Arthroscopic evaluation, nonetheless, is subjective and limited to the surface of AC. Moreover, no generally accepted arthroscopic scoring system of cartilage degeneration in OA is currently available. The semi-quantitative system recommended by the International Cartilage Repair Society (ICRS) was originally developed for classifying severity of traumatic chondral [8] , albeit later has been widely used similarly to assess degeneration of AC. In ICRS grading, cartilage defects are classified into four stages based on the lesion depth.

Although degeneration of cartilage is the hallmark of OA, the disease affects simultaneously numerous joint structures. Thus, for comprehensive characterization of the joint a whole-organ evaluation schemes, such as the Whole Organ Arthroscopic Knee Score (WOAKS) [44] , have been developed. WOAKS consists of the sum of the total cartilage ICRS score and the total

grade of meniscus lesions, classified regarding to the extent of needed surgical resection in all joint subregions.

Magnetic resonance imaging (MRI) has increasingly been used as a non-invasive diagnostic modality of OA and it provides information on tissue changes prior to radiographic changes [6, 15, 25, 40]. T_2 relaxation time is sensitive to the integrity of the collagen network, collagen content and water content [34, 35, 37]. Elongation of T_2 relaxation time has been associated with early cartilage degeneration in vitro [30, 34, 35, 37, 38] and in vivo [14, 25]. The delayed gadolinium enhanced MRI of cartilage (dGEMRIC) technique is based on T_1 relaxation time measurements after intravenous administration of paramagnetic contrast agent gadopentetate ($Gd\text{-}DTPA^{2-}$). Gadopentetate distribution in AC is assumed to be inversely proportional to the fixed charge density due to the negatively charged glycosaminoglycan (GAG) molecules and is reflected in the variation of T_1 relaxation time. Loss of proteoglycans is known to be an early event in the progression of OA and dGEMRIC technique is predictive for future joint degeneration [18, 46]. T_1 relaxation time in the absence of contrast agent reflects the content of MRI-visible water molecules [5], a property known to elevate in OA [32]. In addition to quantitative MRI parameters of AC, semi-quantitative evaluation schemes have also been previously introduced to evaluate whole-organ changes within a joint [20].

Contrary to qMRI, arthroscopy is not specific for cartilage constituents. Nevertheless, it has been widely considered the most accurate diagnostic tool to probe the status of cartilage. This paradigm is based on the evidence that the appearance of degenerated AC is the macroscopic manifestation of biochemical alterations of the extracellular matrix. Further, it is assumed that the extent of such manifestations, i.e. the lesion depth, is in proportion to compositional changes and their progression. Therefore, one should expect an agreement between cartilage loss and qMRI outcomes of remaining cartilage. The aim of this study was to verify this hypothesis and

93 evaluate the accuracy of diagnostic arthroscopy by testing the association between cartilage
94 degeneration, as determined by arthroscopic grading, and qMRI parameters i.e. T_2 relaxation
95 times, dGEMRIC and pre-contrast T_1 relaxation.
96

Materials and Methods

Study subjects

The present study involved ten patients (7 female and 3 male, age range = 40-68 years) eligible for arthroscopic surgery of the knee due to persistent joint pain and mechanical symptoms. Preliminary diagnoses according with international classification of diseases (ICD)-10 comprehended seven case of derangement of meniscus due to old tear or injury (M23.2), current tear of meniscus in two cases (S83.2) and a primary arthrosis of the knee (M17.1). qMRI at 3T (Siemens Skyra, Siemens Healthcare, Germany) was performed prior to arthroscopy.

Magnetic resonance imaging

T_2 relaxation time was measured using a multi-slice multi echo spin echo sequence (TR = 1680ms, five TE's between 13.8 and 69ms, ETL = 5, FOV = 160×160mm^2, 384×384 matrix, 3mm slice thickness). Pre-contrast T_1 relaxation time and dGEMRIC were determined using a single-slice inversion recovery fast spin echo sequence (TR/TE = 4060/8.6ms, eight TIs between 50 and 3900ms, ETL = 8, FOV = 120×120mm^2, 256×256 matrix, 3mm slice thickness). For dGEMRIC, T_1 mapping was repeated 90 minutes after intravenous injection of 0.2 mM/kg of gadopentetate (Gd-DTPA^{2-}, Magnevist^{TM}) and subsequent flexion-extension of the knee for 5 minutes and walking for 5 minutes. For T_1 and dGEMRIC, a single slice was positioned at the center of the medial condyle, and another slice at the center of the lateral femoral condyle. For T_2, seven slices were positioned into each femoral condyle and the centermost slice, corresponding to the location of T_1 and dGEMRIC slices, was analyzed. The automatic slice positioning feature of the scanner was used for standardized slice positioning.

For quantitative analysis, articular cartilage was manually segmented from T_1, T_2, and dGEMRIC anatomical images by a single investigator. T_2 and T_1 relaxation times and

dGEMRIC index (i.e. T_1 relaxation time in the presence of contrast agent) were determined in the two slices, approximately at the center of medial and lateral condyles, at six different knee sites (medial and lateral tibia, medial and lateral femur, medial and lateral trochlea) corresponding to the arthroscopy locations (Figure 1). Relaxation time values were determined for superficial, deep and bulk (i.e. full-thickness) regions-of-interest (ROIs) using an in-house MATLAB application (v.7.9.0; MathWorks inc., Natick, MA, USA). Partial volume effect was minimized by excluding the first voxel at the cartilage surface and cartilage-bone interface from analyses.

To determine the intra-reader reliability, the first authors (V.C.) with 2 years of experience in cartilage segmentation segmented cartilage three times in each relaxation time map. Consequently, the root-mean-square average coefficient of variation (CV_{RMS}) was calculated for each ROI. An error below 10% was considered good while error below 5% were considered very good [2].

To account for the magic angle effect, i.e. orientation dependence of T_2 relaxation time in the B_0 field [42], and for the consequent topographical variation of relaxation times in cartilage [21, 47], T_2 was standardized by normal values determined from a group of healthy volunteers (n = 11, age range = 24-44, imaging parameters as above). Health status of the subjects was confirmed by an experienced radiologist through evaluation of 3D double-echo steady-state images (TR/TE = 14.1/5ms, ETL = 2, flip angle = 25, FOV = 150×150mm^2, 238×256 matrix, 0.6mm slice thickness). Informed consent was obtained from all volunteers.

Quantitative analysis was performed as above and standardized T_2 values (T_{2std}) was calculated for each ROI as follows:

$$T_{2std} = T_2(0,1) \cdot \sigma_h + \langle T_2 \rangle_h ,$$

where $T_2(0,1)$ is normally distributed T_2 from patients obtained subtracting the mean of T_2 from patient values and dividing by its standard deviation, $\langle T_2 \rangle_h$ and σ_h are averages and standard deviations of control subjects, respectively.

Arthroscopy

Arthroscopy was conducted 2-12 weeks after imaging and performed by an experienced surgeon (P.L., 15 years of experience), and cartilage was graded according to the International Cartilage Repair Society (ICRS) classification system at locations of MRI analyses. In ICRS grading scale, normal cartilage is scored with the grade 0 (ICRS0); occurrence of soft indentation stiffness and/or superficial fissures and cracks are awarded a grade 1 (ICRS1); grade 2 (ICRS2) and 3 (ICRS3) are scored in presence of lesions extending up to or more than 50% of cartilage depth, respectively; grade 4 (ICRS4) indicates defects through the subchondral bone.

Institutional review board approval

The study protocol was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District, Oulu, Finland (No. 33/2010). Informed consent was obtained from all subjects.

Statistical analysis

Data from different sites were pooled to test the association between qMRI parameters and arthroscopic grades ICRS0 - ICRS2 using the nonparametric Kruskal-Wallis test. According to the effect sizes reported by Wang and Regatte [48], to achieve power of 0.80 with α at 0.05 the sample size required for T_2 and dGEMRIC are three and eight, respectively. Kolmogorov-Smirnov test was performed to test for the normality of the distribution of qMRI parameters.

Correlation between ICRS grades and MRI parameters was tested using Spearman correlation analysis while the correlation between MRI parameters was tested using Pearson correlation analysis. Statistical analyses were performed using SPSS 21 software (SPSS Inc., Chicago, IL, USA).

175 **Results**

176 The number of sites evaluated with ICRS and qMRI are presented in Table 1. Arthroscopy
177 grading was missing from four sites. The cartilage surface was not completely visible in all
178 MRI slices. The whole medial trochlea was not evaluable in one slice for T_2, T_1 and dGEMRIC,
179 and the medial anterior condyle was only partially visible in four T_1 and dGEMRIC slices. In a
180 single case the automatic slice positioning feature failed the slice positioning and one slice from
181 dGEMRIC scans corresponding to the medial side was excluded.. ICRS grade 3 was excluded
182 from the statistical analysis comparing different groups due to the limited number of regions.

183 The root-mean-square average coefficient of variations for T_1, T_2 and dGEMRIC were 4.95%
184 (range = 2.06 - 7.61%), 5.56% (range = 1.91 - 9.25%) and 6.09% (range = 2.51 - 10.01%)
185 respectively. The reliability was excellent (below 5%) in 48% of ROIs and only in single case
186 the error exceeded 10% (in superficial femur, lateral compartment, CV_{rms} = 10.01% for
187 dGEMRIC).

188 T_2 from healthy volunteers showed significant topographical and depth-wise variations (Table
189 2). T_2 before and after standardization, T_2 and T_{2std}, respectively, showed similar behaviour
190 without significant differences (Figure 2). Mean values for different anatomical sites were
191 significantly different in volunteers group ($p = 0.005$) but not at ICRS0 group.

192 Pre-contrast T_1 and T_2 were found to vary statistically significantly between arthroscopic
193 grades ICRS0-ICRS2, as well as superficial and bulk T_{2std} and superficial dGEMRIC (Table 3).
194 Bulk or deep dGEMRIC, or deep T_{2std} values did not vary significantly. However, there was
195 considerable overlap for each of the qMRI parameters between different ICRS grades. qMRI
196 parameters were not linearly dependent on ICRS grading (Table 4). A mild correlation,
197 however, was found when ICRS0 group was excluded from the analysis (data not shown).

198

199 T_2, T_{2std} and T_1 showed a similar trend with shorter values at ICRS1 as compared to ICRS0
200 and an increasing trend towards higher grades (Fig. 2, Table 3). The behaviour of these
201 parameters showed a linear trend between grades ICRS1 to ICRS3. T_{2std} values were always
202 statistically significantly higher in the superficial layer as compared to the values in the deep
203 layer. T_1 values for superficial and deep ROIs were different for grades ICRS0 and ICRS1 while
204 no significant differences were observed between layers at ICRS grade 2. dGEMRIC values
205 showed a different trend, the deeper layer having higher values than the superficial layer with
206 all ICRS grades.

207 T_2 and T_{2std} were strongly correlated. T_1 and T_{2std} relaxation times showed statistically
208 significant correlation. No associations were found between dGEMRIC and T_1 or T_{2std} (Table
209 5).

210

Discussion

The most clinically relevant finding of this study was that loss of cartilage and the quality of remaining tissue in the lesion site may not be directly associated with each other. Previously, cartilage degeneration has been associated with prolonged T_1 and T_2 relaxation times and shortened dGEMRIC index values as compared to normal tissue [14, 33, 46]. Lesions evaluated by arthroscopic grading have also been found to correspond to increased T_2 foci [8, 9]. In the present study, however, a clear correlation between the qMRI parameters and the arthroscopic grading was not found. In contrast to previous studies, an anomalous behaviour of shorter T_1 and T_2 relaxation time values at early degeneration (ICRS1) were observed. Previously, two former studies have shown likewise neither T_2 [11] or dGEMRIC, both after intra-venous as well as intra-articular injection of gadopentetate [22], correlated with arthroscopy. The fundamental difference between these two techniques, qMRI and arthroscopy, may offer an explanation for the current findings. In arthroscopy, the macroscopic appearance and the amount of tissue are evaluated but it is insensitive to intrinsic molecular changes that are not visible at the cartilage surface. Arthroscopic evaluation is also subjective and dependent on the operator [43]. Contrary to arthroscopy, qMRI visualizes the full thickness of cartilage and provides a quantitative surrogate for alterations in tissue composition and structure, namely collagen network degradation, proteoglycan loss and increase in water content. Such changes are expected to be asymptomatic at early stages of OA, and may also be invisible under arthroscopy. Moreover, in this study the MRI intra-reader reliability was good to excellent and similar results have been reported for patellar cartilage [19, 27]; on the contrary it has been shown only a moderate intra-observer reliability for arthroscopy [7]. Hence, a significant correlation between qMRI and arthroscopy may not be expected.

ICRS grading is based on the depth of AC defects. Such a lesion-based approach, perfectly applicable to traumas, may be limited in case of extensive tissue loss driven by degeneration

236 especially at the end stages of OA. Additionally, although macroscopic evidence such as
237 superficial swelling and fracturing are driven by, and have been also associated with,
238 biochemical changes [4], they become visible in arthroscopy only when the degeneration is at
239 more advanced stages. This view is supported by the mild association found between ICRS
240 grades and qMRI parameters T_1 and T_2 once normal cartilage (ICRS0) was excluded from the
241 analysis. To confirm this, in vivo MRI findings should be correlated with ultrastructural
242 parameters, such as biochemical composition and histological structure.

243 The variations of MRI parameters suggest a better sensitivity to OA progression as compared
244 to arthroscopy. Particularly, T_1 and T_2 correlated significantly and exhibited similar behaviour
245 with an initial decrease followed by a rising after a marked minimum at grade 1. These findings
246 suggest alterations in tissue hydration and the integrity of the collagen network. Such trends
247 may correspond to different stages of OA advancement not detected by arthroscopy. Prolonged
248 T_2 and T_1 relaxation times have been reported in previous studies evaluating osteoarthritic
249 cartilage [13, 29, 38], believed to reflect changes in the collagen network and tissue hydration,
250 respectively [34, 36]. Nonetheless, T_2 shortening at early stages of degeneration has been
251 previously reported in one in vitro and one in vivo studies [11, 38]. These studies together with
252 the current findings suggest that the early stages of OA may involve more complicated
253 alterations in tissue composition than currently understood. The elongation of T_1 and T_2
254 relaxation times at later degeneration stages could then represent the progressive erosion that
255 leads to loss of both cartilage quantity and quality.

256 dGEMRIC was relatively insensitive to detect degenerative changes at different
257 arthroscopic grades. Surprisingly, dGEMRIC index values for grade ICRS0 were of the order
258 of those for radiographic OA, as previously reported by Kimelman et al. [26], implying that
259 ICRS0 grade cartilage may not actually be normal but rather represent tissue with early disease.
260 Additionally, in the present study T_2 values in ICRS0 grade did not show topographical

variation as observed for control subjects, further suggesting that ICRS0 cartilage may not represent healthy tissue. On the other hand, Stubendorff et al. concluded that at early stages of OA cartilage GAG may not be altered to the degree that it is detected by dGEMRIC [45]. Furthermore, synthesis of collagen associated with early OA could be responsible for nonlinear behaviour of tissue properties in the course of degeneration [1, 31, 41]. Such an elevation of collagen concentration could result in shortened T_1 and T_2 values, as observed for ICRS1 cartilage in this study.

Since OA involves all tissues in the joint, a whole-organ evaluation may be more appropriate for clinically describing the status of osteoarthritic knee. In arthroscopic examinations, such a whole-organ score for OA degenerative pathologies does not exist. WOAKS scoring system should be preferably used, although it relies on the ICRS protocol itself for classification of cartilage and bone status. On the other hand, several whole-joint classification systems are currently available for MRI, such as the Whole-Organ Magnetic Resonance Imaging Score (WORMS) [39], the Boston-Leeds Osteoarthritis Knee Score (BLOKS) [24], the Knee Osteoarthritis Scoring System (KOSS) [28] and the MR Osteoarthritis Knee Score (MOAKS)[23], allowing one to simultaneously evaluate all joint structures including cartilage, meniscus, ligaments, subchondral bone and various OA features with different subregional division of knee compartments. Further investigations comparing semi-quantitative MRI-based scoring systems with WOAKS and qMRI are required to provide evidence of their sensitivity to pathological changes in cartilage as well as in other joint structures.

The current study has limitations that need to be discussed. First, the sample size was relatively small and it varied significantly between different degeneration grades being particularly low for ICRS3 grade. This uneven distribution of grades was due to the cross-sectional nature of the study. Second, the co-registration of MRI and arthroscopy was

performed visually using anatomical landmarks, and this approach may result in a degree of error. Third, it is noteworthy that relaxation mechanisms are not affected only by a single constituent, but are likely dependent by several factors. T_2 relaxation time is reported to be sensitive to collagen orientation, collagen content and tissue hydration [34, 35, 37]. dGEMRIC is not only dependent on cartilage GAG but several factors make it not specific for cartilage proteoglycans [12]. The finding that different qMRI parameters behaved in a somewhat different manner with increased cartilage degeneration and were not strongly related (apart from T_2 and T_{2std}) is, however, proof of the fact that the different MRI techniques probe different aspects of the biochemical status of cartilage. Fourth, MRI and arthroscopy were performed at different times and changes in tissue may occur in between, depending on patient diagnoses and time delays, and may in principle affect the prevalence. Finally, the regions analysed in the present study represent various topographical locations. Previous studies have reported topographical variation of relaxation times in cartilage [21, 47]. In the present study, we were only able to standardize T_2 values using data from a small cohort of healthy volunteers. However, T_1 variation between different knee compartments has shown being modest [49], while the strong correlation and the modest differences between T_2 and T_{2std} suggest that the contribution from topographical variation is limited.

The evidence from this study suggests that the quality of AC tissue may not be directly associated with the grade of cartilage loss as assessed through diagnostic arthroscopy.

Conclusion

In conclusion, the severity of cartilage degeneration may not be revealed solely by diagnostic arthroscopy and thus qMRI can have a role in the investigation of cartilage degeneration. Further studies, preferably using histological reference, are required in order to determine whether this discrepancy is due to the superior sensitivity of qMRI to detect degenerative changes in cartilage or the differential sensitivity of qMRI and arthroscopic grading for different aspects of cartilage degeneration.

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Conflict of interest.

The authors declare that they have no conflict of interest.

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460

461 TABLES

462 **Table 1.** Number of regions of interest at different anatomical sites for T_2 and T_1/dGEMRIC

463 with different ICRS grades.

				ICRS grading			
	Site	**Side**	**Total**	**ICRS0**	**ICRS1**	**ICRS2**	**ICRS3**
T_2	**Trochlea**	**Medial**	9	5	2	1	1
		Lateral	9	9	0	0	0
	Tibia	**Medial**	10	0	8	2	0
		Lateral	9	0	5	4	0
	Femur	**Medial**	10	1	1	7	1
		Lateral	9	6	1	2	0
	Total		56	21	17	16	2
T_1	**Trochlea**	**Medial**	6	4	1	1	0
		Lateral	9	9	0	0	0
	Tibia	**Medial**	9	0	7	2	0
		Lateral	9	0	5	4	0
	Femur	**Medial**	9	1	0	7	1
		Lateral	9	6	1	2	0
	Total		51	20	14	16	1

464

Table 2. Means and standard deviations (SD) of T_2 values (ms) from healthy volunteers (N=11).

		T_2		
		Bulk	**Superficial**	**Deep**
Site	**Side**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Trochlea	**Medial**	52.5 (10.2)	54.3 (11.0)	49.1 (10.7)
	Lateral	47.8 (5.4)	56.8 (7.0)	38.4 (5.9)
Tibia	**Medial**	40.9 (3.4)	46.4 (6.4)	33.8 (5.4)
	Lateral	40.0 (5.9)	47.1 (8.3)	32.5 (6.1)
Femur	**Medial**	49.0 (9.9)	54.9 (6.8)	42.2 (15.7)
	Lateral	50.5 (5.1)	57.0 (7.6)	42.3 (10.6)

Table 3. Mean qMRI bulk, superficial and deep values (ms) for different OA grades, and p-values from Kruskal-Wallis test.

		ICRS grading				
		ICRS0	ICRS1	ICRS2	ICRS3	
qMRI parameter	ROI	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p-value
	Bulk	51.3 (6.7)	39.5 (8.5)	44.7 (9.5)	52.2 (6.9)	0.0005
T_2	**Sup**	59.0 (8.8)	47.4 (8.6)	51.5 (11.3)	63.5 (2.1)	0.003
	Deep	44.3 (11.7)	31.9 (9.6)	36.7 (10.7)	38.9 (13.9)	0.001
	Bulk	50.1 (7.0)	42.9 (7.3)	46.0 (9.5)	51.3 (6.1)	0.023
T_{2std}	**Sup**	57.0 (7.7)	49.0 (7.2)	50.2 (8.9)	58.3 (2.5)	0.011
	Deep	42.5 (9.6)	36.0 (10.6)	40.0 (12.8)	37.0 (14.0)	(n.s.)
	Bulk	1425 (256)	1125 (141)	1266 (294)	1653	0.001
T_1	**Sup**	1496 (247)	1326 (152)	1331 (247)	1683	0.033
	Deep	1362 (314)	937 (208)	1217 (393)	1627	0.001
	Bulk	520 (55)	531 (106)	479 (104)	541	(n.s.)
dGEMRIC	**Sup**	464 (72)	479 (95)	406 (74)	426	0.021
	Deep	565 (76)	590 (152)	570 (128)	644	(n.s.)

ROI = Region of interest. Sup = Superficial. Grade 3 was excluded from the test due to the small amount of regions.

471 **Table 4.** Spearman's correlation coefficients (ρ) with 95% confidence intervals between MRI
472 parameters and ICRS grades in bulk, superficial and deep cartilage ROIs, separately presented
473 for ICRS grades 0-3 (N=51-56).

		Bulk	Superficial	Deep
	qMRI parameter	**ρ (95% CI)**	**ρ (95% CI)**	**ρ (95% CI)**
ICRS 0-3	**T_2**	-0.25 (-0.48, 0.01)	-0.19 (-0.43, 0.08)	-0.29 (-0.52, -0.03)*
	T_{2std}	-0.16 (-0.40, 0.11)	-0.25 (-0.48, 0.02)	-0.10 (-0.36, 0.17)
	T_1	-0.19 (-0.44, 0.09)	-0.26 (-0.50, 0.02)	-0.12 (-0.38, 0.16)
	dGEMRIC	-0.19 (-0.44, 0.10)	-0.30 (-0.53, -0.02)*	0.06 (-0.22, 0.34)

* $p < 0.05$

474

475 **Table 5.** Pearson's correlation coefficients (r) with 95% confidence intervals between MRI

476 parameters in bulk cartilage ROIs (N=50-59).

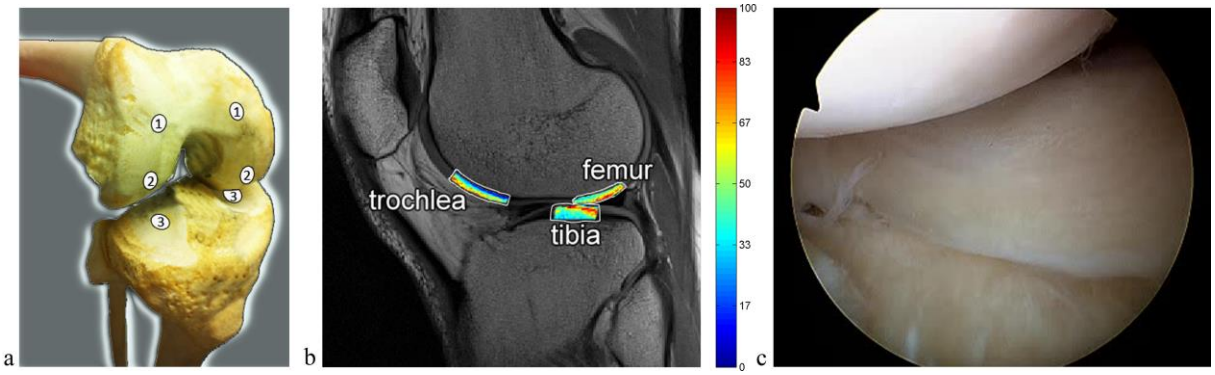
	$T_{2,std}$	T_2	T_1
	r (95% CI)	**r (95% CI)**	**r (95% CI)**
T_2	0.93 (0.88, 0.96)**		
T_1	0.43 (0.19, 0.63)**	0.53 (0.31, 0.70)**	
dGEMRIC	-0.24 (-0.48, 0.03)	-0.18 (-0.43, 0.10)	-0.25 (-0.50, 0.03)

* $p < 0.05$, ** $p < 0.01$

477

478 FIGURES

479



480

481 **Figure 1.** (a) Anatomical locations of trochleal (1), femoral (2) and tibial (3) ROIs. (b) Corresponding
482 locations of ROIs at the lateral compartment on T_2 relaxation time map. (c) Arthroscopic view of tibia
483 (ICRS grade 2) and femur (ICRS grade 0).

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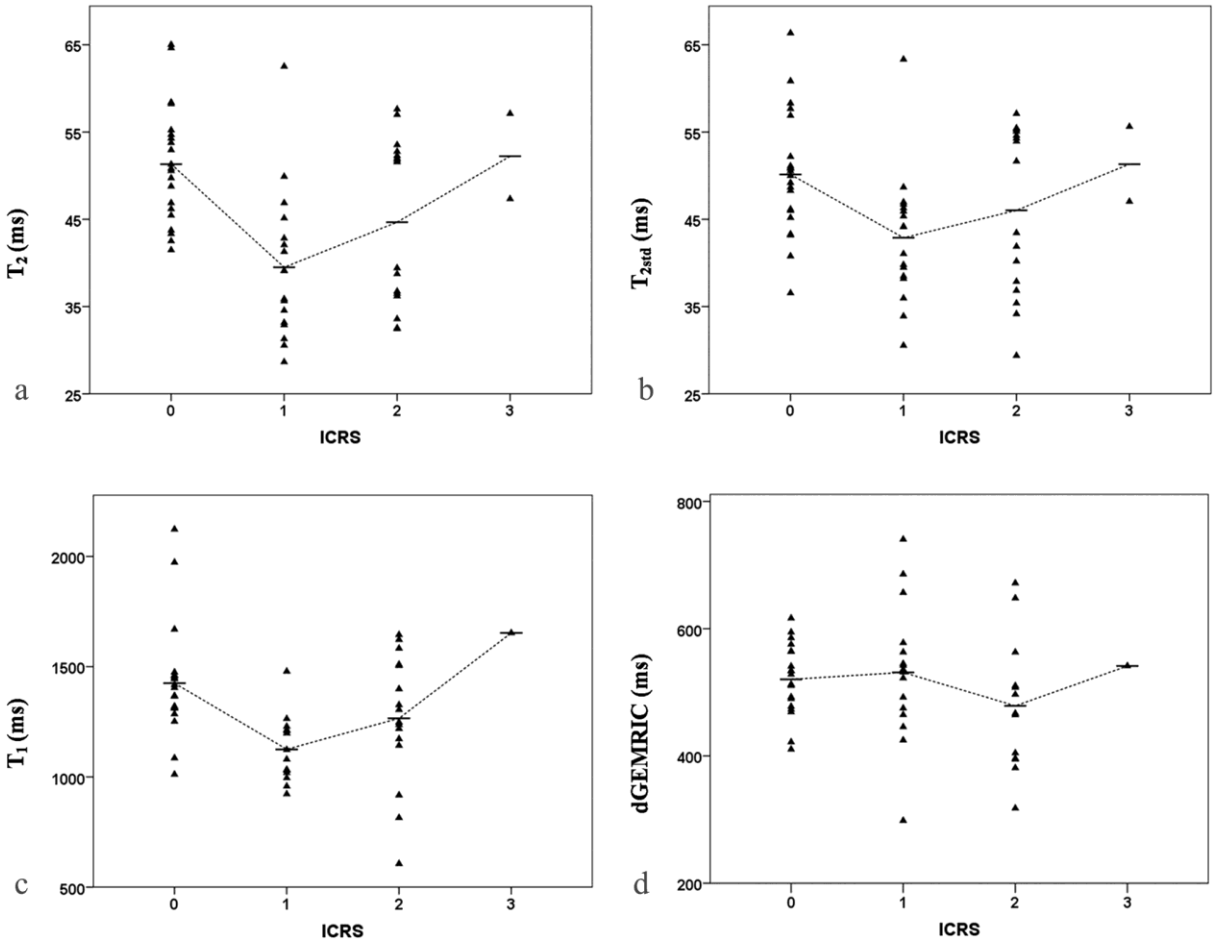

Figure 2. Bulk values of T_2 (a), T_{2std} (b), T_1 (c) and dGEMRIC (d) as a function of ICRS grading (ICRS grade 3 is shown only for illustrative purpose).