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Biochemical MRI Predicts Hip Osteoarthritis in an Experimental Ovine Femoroacetabular Impingement Model

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Abstract

Background Cam-type femoroacetabular impingement (FAI) resulting from an abnormal nonspherical femoral head shape leads to chondrolabral damage and is considered a cause of early osteoarthritis. A previously developed experimental ovine FAI model induces a cam-type impingement that results in localized chondrolabral damage, replicating the patterns found in the human hip. Biochemical MRI modalities such as T2 and T2* may allow for evaluation of the cartilage biochemistry long before cartilage loss occurs and, for that reason, may be a worthwhile avenue of inquiry.

Questions/purposes We asked: (1) Does the histological grading of degenerated cartilage correlate with T2 or T2* values in this ovine FAI model? (2) How accurately can zones of degenerated cartilage be predicted with T2 or T2* MRI in this model?

Methods A cam-type FAI was induced in eight Swiss alpine sheep by performing a closing wedge intertrochanteric varus osteotomy. After ambulation of 10 to 14 weeks, the sheep were euthanized and a 3-T MRI of the hip was performed. T2 and T2* values were measured at six locations on the acetabulum and compared with the histological damage pattern using the Mankin score. This is an established histological scoring system to quantify cartilage degeneration. Both T2 and T2* values are determined by cartilage water content and its collagen fiber network. Of those, the T2* mapping is a more modern sequence with technical advantages (eg, shorter acquisition time). Correlation of the Mankin score and the T2 and T2* values, respectively, was evaluated using the Spearman's rank correlation coefficient. We used a hierarchical cluster analysis to calculate the positive and negative predictive values of T2 and T2* to predict advanced cartilage degeneration (Mankin ≥ 3).

Results We found a negative correlation between the Mankin score and both the T2 ($p < 0.001$, $r = -0.79$) and T2* values ($p < 0.001$, $r = -0.90$). For the T2 MRI technique, we found a positive predictive value of 100% (95% confidence interval [CI], 79%–100%) and a negative predictive value of 84% (95% CI, 67%–95%). For the T2* technique, we found a positive predictive value of 100% (95% CI, 79%–100%) and a negative predictive value of 94% (95% CI, 79%–99%).

Conclusions T2 and T2* MRI modalities can reliably detect early cartilage degeneration in the experimental ovine FAI model.

Clinical Relevance T2 and T2* MRI modalities have the potential to allow for monitoring the natural course of osteoarthrosis noninvasively and to evaluate the results of surgical treatments targeted to joint preservation.

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Each author certifies that his or her institution approved the animal protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research.

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Introduction

Cam-type femoroacetabular impingement (FAI) resulting from an abnormal nonspherical femoral head shape in human hips leads to chondrolabral damage and is considered a cause of early osteoarthritis [1, 4, 19]. Localized areas of cartilage lesions in sheep hips, similar to the findings in human hips with cam-type impingement, are reproduced in an experimental ovine FAI model [16]. The sheep have been chosen as a model because ovine hips bear a strong anatomic resemblance to the human hip. Similarities include a horseshoe-shaped acetabular cartilage with a central fossa and the presence of a circumferential labrum [15]. In the sheep, an experimental cam-type conflict can be induced by rotating the physiological nonspherical femoral head toward the acetabular rim [16]. Medial rotation of the femur is created by performing a closing wedge varus osteotomy and plating of the proximal femur. With free ambulation of the sheep, this cam-type deformity results in posterosuperior acetabular cartilage damage in deep flexion [16]. After a mean ambulation period of 18 weeks, histologically confirmed cartilage lesions averaging a Mankin score of 4 (range, 3–7) were found [16]. The Mankin score describes the histological cartilage degeneration based on structure, cellularity, staining, and tidemark integrity. This ordinal score ranges from 0 (healthy cartilage) to 14 (end-stage degeneration).

Novel biochemical MRI modalities may allow evaluation of cartilage biochemistry long before cartilage loss occurs [5, 10]. Among others, noncontrast biochemical MRI techniques include T2 and T2* mapping sequences [6–9]. T2 and T2* relaxation time mapping is sensitive for the cartilage water content and collagen fiber orientation. A decrease in T2 or T2* values indicates loss of water content and cartilage degeneration. Of these two MRI sequences, T2* mapping is the more modern sequence with technical advantages (eg, faster acquisition time, high resolution, ability of isotropic three-dimensional evaluation) but with a lack of normative data or a standardized acquisition protocol [6].

Clinically, these novel biochemical MRI techniques allow monitoring of cartilage degeneration and evaluation of the effectiveness of surgical or nonsurgical treatment for cartilage regeneration. In research applications, these techniques may eliminate the need to euthanize animals to ascertain the extent of cartilage damage. However, these MRI techniques have not previously been correlated with the histological grading of cartilage degeneration in this animal model.

We therefore asked: (1) Does the histological grading of degenerated cartilage using the Mankin score correlate with T2 or T2* values for the established ovine FAI model? (2) How accurately can zones of degenerated cartilage be predicted with T2 or T2* MRI in this model?

Materials and Methods

Permission was obtained from the local veterinary board to perform this work (Kantonales Veterinäramt Zürich, application No. 123/2006). The study was performed in accordance with the Swiss national laws of animal welfare and protection. Eight female sheep with an age between 2 and 2.5 years and a weight between 50 and 62 kg were included in this study. A cam-type impingement was experimentally induced by a unilateral intertrochanteric 15° varus osteotomy with a medial closing wedge resection (Fig. 1A). The osteotomy of the proximal femoral shaft was performed just above the lesser trochanter without entering the hip. A 15° varus osteotomy has been found to be sufficient to create an impingement conflict eventually resulting in a cartilage damage pattern comparable to the one found in human FAI hips [16]. The operated side was randomly chosen and the contralateral side was used as a control for comparative histological grading. In a previous study with the proposed ovine FAI model, a mean duration of ambulation of 18 weeks (range, 14–22 weeks) after the varus intertrochanteric osteotomy resulted in a mean Mankin score of 4 (range, 3–7). To investigate early degenerative changes of the acetabular cartilage, a mean ambulation period of 12 weeks (range, 10–14 weeks) was chosen for the sheep in the current study.

The same treatment protocol and surgical procedure was applied as described earlier [16]. In short, the sheep were placed in the lateral recumbent position on the contralateral side. A posterior curved skin incision anterior to the greater trochanter was performed (Fig. 2). To expose the femur, the origin of vastus lateralis and intermedius muscles was partially released. A horizontal cut was performed at the level right above the lesser trochanter (Fig. 2). The

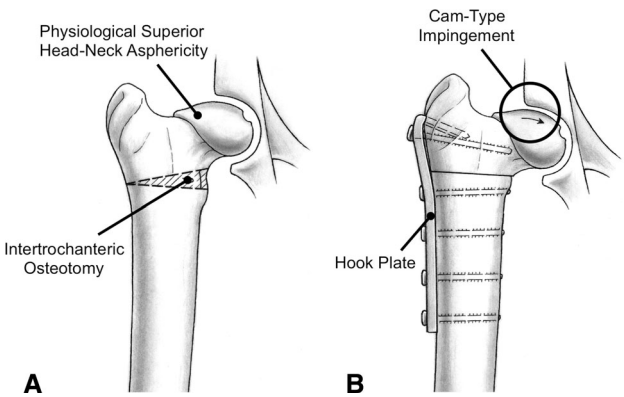

Fig. 1A–B (**A**) The sheep hip has a physiological head-neck asphericity in the superior part of the joint. (**B**) A cam-type impingement can be created by medial rotation of the head and neck after an intertrochanteric osteotomy with a medial 15° closing wedge resection.

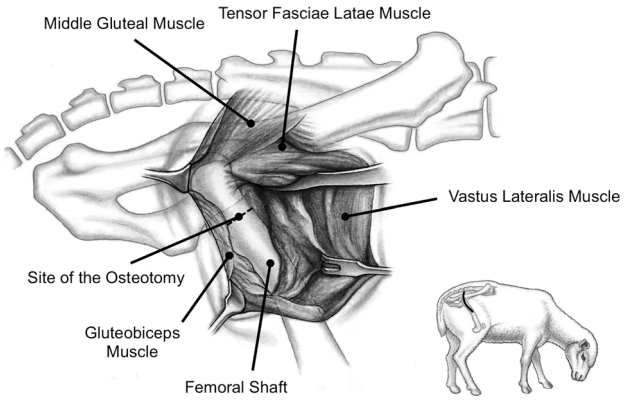

Fig. 2 Surgical approach to the proximal femur of the sheep. A posterior curved skin anterior to the greater trochanter is performed. To expose the femur, the origin of vastus lateralis and intermedius muscles was partially released. A horizontal cut was performed at the level right above the lesser trochanter.

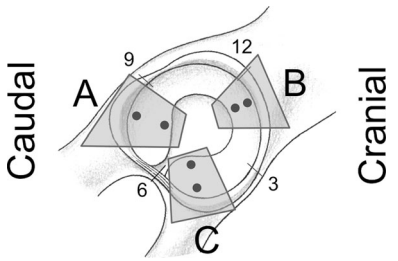

Fig. 3 Histological grading of cartilage and T2 and T2* measurements was performed at six locations on the acetabulum. In each of the three Sectors A, B, and C, one measurement was performed close to the inner (central) and one close to the outer acetabular rim (peripheral). Area A = posterosuperior (7–9 o'clock); B = cranial (12–2 o'clock); and C = anteroinferior (4–6 o'clock). Six o'clock was defined as the incisura acetabuli. For reasons of comparison, all these were described as if they were right hips. Reprinted with permission from Siebenrock KA, Fiechter R, Tannast M, Mamisch TC, von Rechenberg B. Experimentally induced cam impingement in the sheep hip. *J Orthop Res.* 2013;31:580–587 (Fig. 6). Copyright © 2012 Orthopaedic Research Society.

integrity of the joint was preserved by not lacerating the hip capsule. The correct rotational alignment was ensured by two reference Kirschner wires above and below the osteotomy. The 15° wedge angle was defined by an angle measurement device and the second cut aiming medially and distally was performed (Fig. 1A). The osteotomy was fixed by a double hook plate (Fig. 1B; Synthes, Oberdorf, Switzerland). Interfragmentary compression was obtained by two eccentrically drilled compression screws. The muscles were reattached, the wounds closing in layers in a routine manner, and AP and lateral radiographs were taken to evaluate the postoperative result. Postoperatively, the sheep were immediately placed in a stable suspension device. Adequate pain medication was administrated and supervision was provided until the sheep demonstrated full consciousness. The sheep were kept in the suspension device for 3 weeks to ensure bone healing and protected weightbearing. After another 3 weeks in a small stable, the sheep were allowed to roam free.

After the assigned ambulation period of 10 to 14 weeks, the sheep were euthanized. To avoid metal artifacts in the MRI, the double hook plate was removed using the same surgical approach as described previously. The hips were harvested without damaging the joint capsule. MRI of the hips was performed followed by histological evaluation of the cartilage. Six locations of measurement on the acetabulum were defined (Fig. 3). Three sectors of the acetabulum were defined: Sector A posterosuperior (7–9 o'clock), Sector B cranial (12–2 o'clock), and Sector C anteroinferior (4–6 o'clock; Fig. 3). In each of the three sectors, one measurement was performed close to the inner (central) and one close to the outer acetabular (peripheral) rim (Fig. 3). Six o'clock was defined as the acetabular notch. For reasons of comparison, all hips were described as if they were right hips with 3 o'clock being ventral.

The MRIs were carried out on a Siemens 3-T MRI scanner (Trio®; Siemens Medical AG, Erlangen, Germany) with an eight-channel knee coil (SENSE® Knee Coil 3.0 T, 8 Channel Phase Array Coil; Invivo, Gainesville, FL, USA). A localizer was used and protocols were equal to the in vivo protocols in human beings except with a smaller field of view and a higher resolution. This was chosen as a result of the smaller dimensions of the ovine hip and cartilage. An isotropic three-dimensional true fast imaging sequence with steady-state precession (field of view 160, TR [repetition time] 8.01, TE [echo time] 3.47, 1.2 × 1.2 × 1.2 mm) was performed to assess the entire joint and was used as a localizer to plan the biochemical sequences. The radial slices were oriented orthogonal to the femoral neck axis and perpendicular to the acetabular cartilage. We used the same anatomical reference coordinate system as for the histological analysis, ie, 6 o'clock defined by the acetabular notch. These slices were planned individually for each sheep hip on a Siemens workstation (Leonardo® Workstation; Siemens Medical AG). Two high-resolution biochemical cartilage-sensitive sequences (T2 [Fig. 4A] and T2* [Fig. 4B]) were obtained at the same previously defined imaging positions.

A specific protocol was used for T2 (two-dimensional spin echo; multicontrast; TR 597 ms; TE 14.3, 28.6, 42.9, 57.2, 71.5, and 85.8 ms; flip angle 180°, base resolution 512, band width 130 HzPx-1) and T2* (two-dimensional gradient echo; TR 132 ms; TE 4.6, 10.88, 17.16, 23.4, 29.6, and 36.0 ms; flip angle 30°, base resolution 512, band width 160 HzPx-1). The acquisition time was 55 minutes 9 seconds using three repetitions for the T2 and 38 minutes

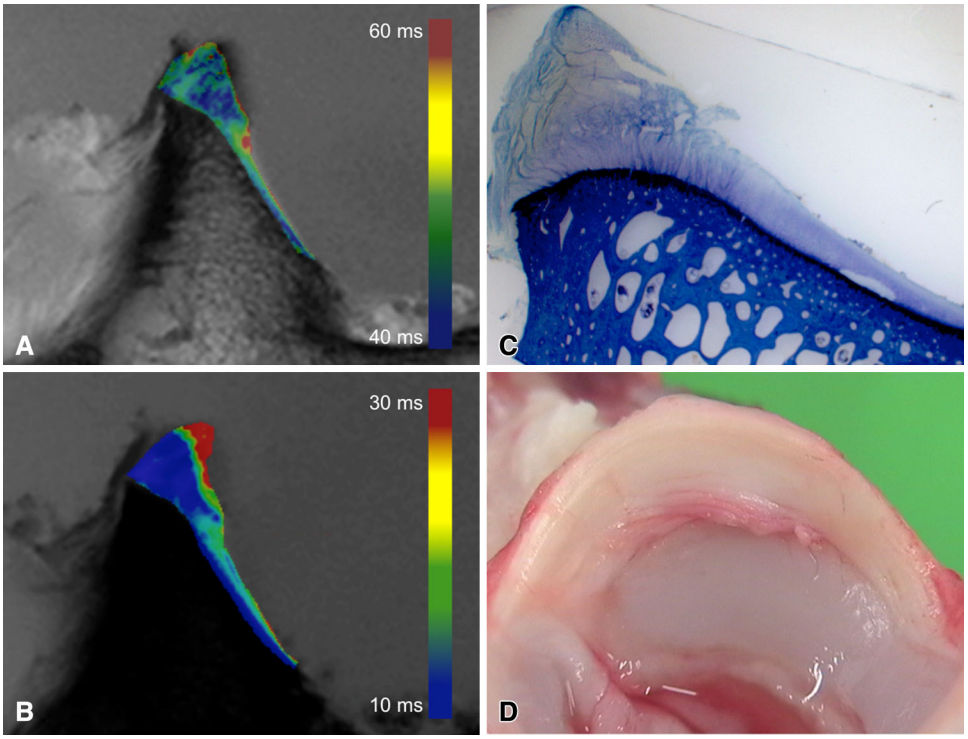

Fig. 4A–D (**A**) The T2 and (**B**) T2* images of an acetabular cartilage of a sheep 14 weeks after surgical FAI induction are shown. Biochemical MRI techniques such as the T2 and T2* sequence are based on the fact that early changes in cartilage water content and the collagen orientation alter the MRI signals [5]. The T2 and T2* values are color-coded and mapped the gray scale conventional morphologic sequence. The sequences are radially oriented around the femoral neck and therefore the cartilage is cut perpendicular. (**C**) Toluidine blue staining was performed for grading of the cartilage lesion according to Mankin [11, 12]. (**D**) The macroscopic image shows alterations of the chondrolabral junction in the posterosuperior area of the acetabulum.

15 seconds using six averages for the T2*. Magic angle artifact was controlled by positioning the specimen in the MR scanner. We empirically avoided an angle of approximately 55° of the cartilage region of interest. In a subset of specimens, coronal T2* maps were acquired in addition and results matched exactly. In this setting we did not observe magic angle artifacts to an extent that could significantly influence our results.

The images were transferred to a Siemens Leonardo Workstation (Leonardo® Workstation; Siemens Medical AG). The T2 and T2* values were measured on the radial sequences at 8, 1, and 5 o'clock (Fig. 3), which represent the centers of the sectors A, B, and C, respectively. Each section was further subdivided into a peripheral and central portion, resulting in six measurements for each of the eight sheep (48 measurements in total). After disarticulation and removal of the periarticular soft tissues, regions of interest of the acetabular cartilage were defined for each measurement by consensus of two observers (KAS, TCM).

After MR imaging, bone-cartilage samples from each Sector A, B, and C with dimensions of 1.5 × 3.5 cm were harvested using an oscillating saw. Each sample included areas of the acetabular fossa, cartilage with subchondral bone, and the acetabular rim with the labrum. All samples were fixed immediately in 4% paraformaldehyde for 24 to 48 hours and then underwent toluidine blue staining (Fig. 4C). Cartilage degeneration was graded according to the Mankin score [11, 12], which was assessed blinded to the T2 and T2* values (Fig. 4A–B). The reliability and reproducibility of the Mankin score has been reported previously [18]. The contralateral side was used as a control for comparative histologic grading according to Mankin [11, 12]. Comparing the control hip and the hip with FAI, there was an increased Mankin score posterosuperior (Fig. 4D) and anteroinferior for the hip with FAI (Table 1). These differences are comparable with previous results and confirm the experimental ovine FAI model [16].

Correlation of the Mankin score and the T2 and T2* values, respectively, was evaluated using the Spearman's rank correlation coefficient. Using Ward's method for hierarchical cluster analysis [20], we grouped the Mankin score, the T2, and T2* values independently into clusters with advanced or no/little cartilage degeneration. The statistically determined threshold for advanced cartilage lesions was a Mankin score ≥ 3. Ninety-four percent of all

Table 1. The Mankin score and, the T2 and T2* values for the six locations of measurement on the acetabulum are summarized

Parameter	Group	Location					
		Peripheral			Central		
		A (posterosuperior)	B (cranial)	C (anteroinferior)	A (posterosuperior)	B (cranial)	C (anteroinferior)
Mankin score	FAI	5.1 ± 1.4 (3–7)	0.9 ± 1.7 (0–5)	4.1 ± 2.2 (2–8)	0.6 ± 0.7 (0–2)	0.1 ± 0.4 (0–1)	0.3 ± 0.7 (0–2)
	Control	1.3 ± 1.2 (0–3)	0.6 ± 0.7 (0–2)	1.6 ± 1.9 (0–5)	0.3 ± 0.7 (0–2)	0	0.5 ± 0.9 (0–2)
	p value	< 0.001	0.428	0.033	0.087	0.317	0.535
T2 value (ms)	FAI	50 ± 2 (47–53)	55 ± 3 (50–58)	49 ± 3 (42–52)	56 ± 2 (52–59)	57 ± 2 (55–59)	55 ± 2 (51–58)
T2* value (ms)	FAI	16 ± 2 (14–20)	24 ± 4 (16–27)	17 ± 4 (13–24)	24 ± 2 (20–26)	26 ± 1 (24–28)	24 ± 2 (21–27)

Values are expressed as mean ± SD and range in parentheses; FAI = femoroacetabular impingement.

samples with advanced histological cartilage lesions were found in the peripheral area of Zone A and C. Based on this dichotomous allocation, we then calculated the positive and negative predictive values of T2 and T2* to predict the actual histological damage (Mankin score).

Results

We found that histological damage was negatively correlated with T2 ($p < 0.001$, $r = -0.79$) and T2* values ($p < 0.001$, $r = -0.90$) (Fig. 5).

For the T2 MRI technique, we found a positive predictive value of 100% (95% confidence interval [CI], 79%–100%) and a negative predictive value of 84% (95% CI, 67%–95%) to detect advanced cartilage lesions. For the T2* technique, we found a positive predictive value of 100% (95% CI, 79%–100%) and a negative predictive value of 94% (95% CI, 79%–99%).

Discussion

Cam-type FAI has been recognized as a major cause of early osteoarthritis [1, 4, 19]. The typical localized areas of cartilage damage in cam-type FAI could be reproduced in an experimental ovine FAI model [16]. The aim of this study was to investigate if the relaxation times of two biochemical MRI modalities (T2 and T2*) correlate with the early localized cartilage degeneration based on the histological gold standard (the Mankin score). We found a correlation with histological cartilage degeneration for both sequences. In addition, T2 and T2* were found to have a high positive and negative predictive value for detecting histologically advanced cartilage lesions.

This study has several limitations. First, the chondral lesions are created in an animal model and the severity of lesions and/or intensity of MRI signal changes may differ in humans. However, both the macroscopic lesions and the

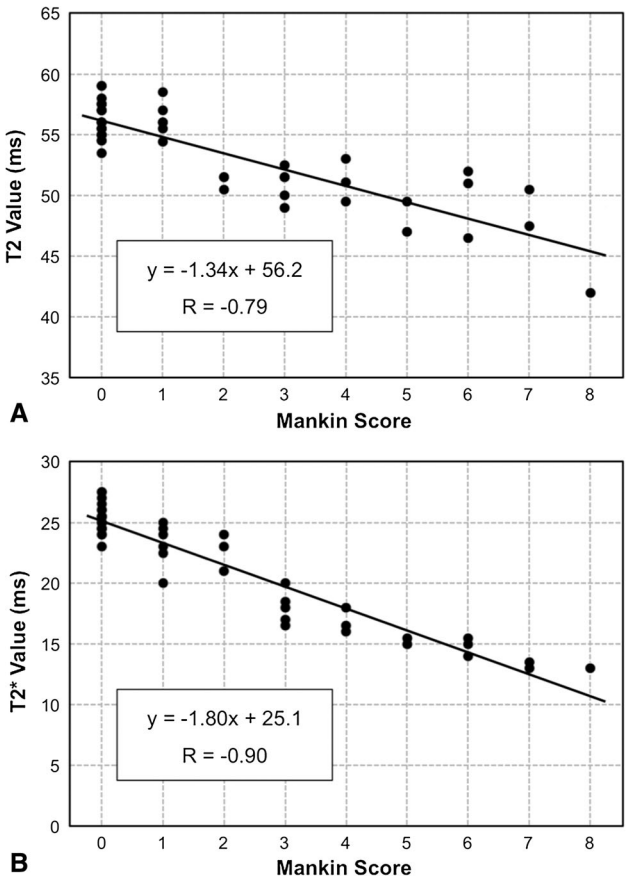

Fig. 5A–B Scatterplot of the Mankin score versus the T2 (**A**) and T2* (**B**) values, respectively, is shown. Both the T2 and T2* values showed a negative correlation with the histological grading of cartilage damage using the Mankin score (both $p < 0.001$; $r = -0.79$ and $r = -0.90$, respectively).

T2 and T2* values in our study were comparable to findings in human hips with early osteoarthritic changes [1, 6]. Second, we did not evaluate other biochemical MR modalities to detect early cartilage lesions including delayed gadolinium enhanced MRI of cartilage (dGEMRIC) or T1ρ. dGEMRIC was not possible because it

requires intravenous contrast agent in vivo. We omitted this technique because it would have implied additional anesthesia of the animals. The T1ρ technique became available in our institution only after completion of the experiments. Third, our analysis focused on the acetabular cartilage only. The acetabular cartilage typically is affected first in hips with FAI and therefore was of primary clinical importance.

Both the T2 and the T2* technique showed a negative linear correlation with the histological evaluation of degeneration (Fig. 5). Although our values for the healthy ovine cartilage for the T2* technique compare well with the reported data in human beings, the normative values for T2 are somewhat lower. We found a normative mean of 25 ms for the T2* relaxation time in sheep. The corresponding reported values in human beings were 23 to 30 ms [13] and 32 ± 4.5 ms [2]. In contrast to the suggested nonlinear T2* response to cartilage degeneration in human beings [3], we found a very linear correlation with a high correlation coefficient. One explanation might be that we used the entire ordinal scale of the Mankin score for calculation of the correlation, whereas in human beings, groups of Makin scores were used [3]. Our normative T2 relaxation time averaged 56 ms, which is considerably higher in comparison to healthy human volunteers (21–40 ms [14], 30 ± 7 ms [13]).

MRIs using T2 and T2* techniques are able to predict the zones of advanced degenerative cartilage with a very high probability (100%) in this ovine FAI model. Analogously to the original description [16], these zones were typically located in the posterosuperior Sector A of the acetabulum. This was the predicted location for cam-type impingement in sheep with a quadripedal gait [16]. Both techniques reliably identified all zones with advanced histological cartilage degeneration, resulting in a positive predictive value of 100%. The current study revealed lower Mankin scores of the involved sectors with cartilage lesions in comparison to the original description [16]. This can be explained by the shorter mean postoperative ambulation period of 12 weeks compared with 24 weeks in the previous study [16]. Shorter ambulation periods were chosen in the present study to create predominantly mild to moderate cartilage lesions as would be expected in early stages of cam FAI-related osteoarthritis. A successful joint-preserving therapeutic intervention in human beings depends on early detection of cartilage degeneration [17]. These novel biochemical MRI techniques may provide a means by which to monitor the natural course of osteoarthrosis noninvasively and to evaluate the results of surgical treatments targeted at joint preservation.

The findings of this study support that T2 and T2* MRI modalities can reliably detect cartilage degeneration in an experimental ovine FAI model. The results of the current study serve for future studies monitoring the natural history of cam-FAI related hip osteoarthritis and its potential treatments options using the proposed ovine FAI model.

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