The Knee 26 (2019) 555–563

Contents lists available at ScienceDirect

The Knee

# Comprehensive description of T2 value spatial variations in non-osteoarthritic femoral cartilage using three-dimensional registration of morphological and relaxometry data

Shannon N. Edd [a,*], Hugo Babel [a], Nadia Kerkour [b], Brigitte M. Jolles [a], Patrick Omoumi [b], Julien Favre [a]

[a] Department of Musculoskeletal Medicine (DAL), Lausanne University Hospital (CHUV), Lausanne, Switzerland
[b] Department of Diagnostic and Interventional Radiology, Lausanne University Hospital (CHUV), Lausanne, Switzerland

ARTICLE INFO

*Article history:*
Received 5 July 2018
Received in revised form 31 January 2019
Accepted 17 March 2019

*Keywords:*
Magnetic resonance imaging
Knee
Cartilage, articular
Computing methodologies

ABSTRACT

*Purpose:* The aim of this study was to develop and assess a method of quantifying cartilage T2 relaxation times in a series of volumes of interest (VOIs) covering the entire cartilage of the femoral condyles. Subsequently, the method was used to test for T2 spatial variations in non-osteoarthritic (OA) knees.
*Methods:* Ten non-OA subjects (five female, average 30 years) were enrolled after informed consent. Three-dimensional bone and cartilage models were created by double echo steady state (DESS) morphological magnetic resonance image (MRI) segmentation, and the models were semi-manually registered with multi-slice, multi-echo (MSME) T2 MRI. Mean T2 values were calculated for 12 VOIs derived from cartilage thickness literature and their respective superficial and deep layers.
*Results:* Analyses showed that intra- and inter-rater reliabilities of the presented method were "good" to "excellent" in more than 90% of the VOIs. Additionally, several spatial differences in T2 values were observed, including, for the medial condyle, higher T2 values in the anterior and central VOIs versus in the posterior VOI ($p < .05$). T2 values were also generally higher in the superficial versus deep layers ($p < .05$).
*Conclusions:* The presented MRI T2 analysis method is reliable and provides a comprehensive quantification of spatial heterogeneity of healthy cartilage compositional properties. This method can be further applied to better understand knee OA pathophysiology and potentially define clinically relevant diagnostic features of the disease.


## 1. Introduction

Knee osteoarthritis (OA) is a debilitating joint disease marked by the degradation and loss of articular cartilage tissue [1]. Measurement of T2 relaxation time with magnetic resonance imaging (MRI) is a well-accepted approach to non-invasively characterize the compositional properties of cartilage [2] by providing information regarding water content [3–5], collagen content [6], as well as the structural organization of cartilage [2]. T2 mapping techniques can thus provide markers of cartilage health, even in the absence of cartilage substance loss [2]. Therefore, the analysis of cartilage compositional data could allow for an improved understanding of the pathophysiology of tibiofemoral OA, a prerequisite of the development of efficient therapeutics, the

* Corresponding author at: Department of Musculoskeletal Medicine (DAL), Lausanne University Hospital (CHUV), Hôpital Nestlé – Swiss BioMotion Lab, Avenue Pierre-Decker 5, CH-1011 Lausanne, Switzerland.
*E-mail address:* shannon-nicole.edd@chuv.ch (S.N. Edd).

https://doi.org/10.1016/j.knee.2019.03.006
0968-0160/

identification of markers for early OA changes, or a means of assessing disease treatments [7]. However, to date, there is a lack of standardized methods to comprehensively quantify and compare T2 values between knees.

To date, tibiofemoral cartilage T2 relaxation time has been mainly quantified using mean values over a few volumes of interest (VOIs) defined on single MRI [8–13], or compartmental T2 relaxation times calculated by averaging the T2 values of successive images [14,15]. A few recent studies have indicated that there are spatial variations in T2 [16–20], supporting a need for methods to quantify T2 in VOIs covering the entire cartilage. Examining methods that have been extensively applied to the analysis of cartilage thickness provides essential guidance for designing more comprehensive T2 analysis methods [21–23]. In particular, the use of average thickness values in standard regions of interest [22,24] have helped improve the understanding of both healthy [23] and OA cartilage [21,22]. Furthermore, previous reports emphasize the importance of examining regions covering the entire tibiofemoral cartilage, as changes occur throughout the cartilage [21–23,25,26]. These principles would also likely be beneficial to the analysis of cartilage compositional data.

An important consideration when analyzing cartilage T2 maps is the identification and segmentation of cartilage tissue. Multi-slice, multi-echo (MSME) T2 imaging sequences provide little contrast between cartilage and the surrounding tissues, and thus, it is preferred to identify cartilage on morphological MRI sequences [14,16,17,27]. Registration between the morphological and compositional data is therefore necessary. Current T2 analyses either disregard this registration step, thus introducing error due to potential subject movement between acquisitions [14,16], or register morphological and compositional MRIs based on image intensity [17,27]. Interestingly, cartilage thickness analyses typically utilize three-dimensional (3D) bone and cartilage models produced by segmentation of morphological MRI sequences [28]. For consistency across morphological and compositional cartilage analyses, these models could be registered to visible features in the MSME images, thus serving to register the morphological and compositional data and identifying cartilage tissue in the MSME sequences.

Therefore, the primary aim of this study was to develop and assess a method to quantify T2 relaxation times in VOIs consistent with the extensive femoral cartilage thickness literature. The method aimed to include the registration of 3D bone and cartilage models from the morphological MRI sequence to the compositional MRI sequence in order to identify the cartilage boundaries. Because quantification of T2 relaxation times using a series of VOIs covering the entire femoral condyles is new, a first step toward the justification of such measures is confirming that there are spatial variations in non-OA knees. Therefore, the secondary aim was to test the hypothesis that T2 relaxation times differ between VOIs in non-OA knees.

## 2. Methods

### 2.1. Subject population

Asymptomatic subjects were recruited for this prospective study approved by the ethics committee and enrolled after written informed consent. The main inclusion criteria were an absence of clinical knee symptoms and any sign of internal derangement of the joint on clinical MRI, as determined by an experienced musculoskeletal radiologist. Ten subjects were included in the study (five female), with an average body mass index (BMI) of 22.4 (range 19.5–25.8) kg/m$^2$ and an average age of 30 (range 25–38) years.

### 2.2. Imaging protocol

Knee imaging was acquired on a 3-Tesla MRI scanner (Magnetom Prisma, Siemens Healthcare, Erlangen, Germany), using a transmit/receive (Tx/Rx) 15-channel knee coil (Quality Electrodynamics, OH, USA). Two MRI sequences were used: a double echo steady state (DESS) morphological sequence (repetition time (TR) = 14.84 ms; echo time (TE) = 5.04 ms; 256 × 240 matrix size; voxel size 0.6 × 0.6 × 0.6 mm) and a multi-slice, multi-echo (MSME) T2 sequence (TR = 1630 ms; TE = 13, 26, 39, 52, 65, 78; 640 × 640 acquisition matrix; interpolated voxel size of 0.3 × 0.3 × 3 mm). T2 relaxation time maps were computed using pixel-by-pixel monoexponential fittings to the signal intensity of echoes two through six of the MSME images, excluding the first echo in order to minimize the effect of stimulated echoes [20,29].

### 2.3. Image analysis

The MRI data were analyzed in three steps as detailed below and illustrated in Figure 1.

#### 2.3.1. Step 1: Segmentation and reconstruction of bone and cartilage models

For each femur, cartilage and bone boundaries were semi-manually segmented with B-spline contours on the DESS images using in-house software. This yielded two 3D models, one of bone and one of cartilage [28].

#### 2.3.2. Step 2: Bone and cartilage model registration to T2 images

To identify the voxels of the T2 images belonging to cartilage, it was necessary to register the DESS-based bone and cartilage models with the T2 MSME images. An initial registration was performed using the spatial information included in the DESS and MSME DICOM headers (Figure 2(a), (b)). The position and orientation of the models was then manually tuned using custom software such that the bone and cartilage models matched these structures as depicted in the MSME first echo images and in the T2

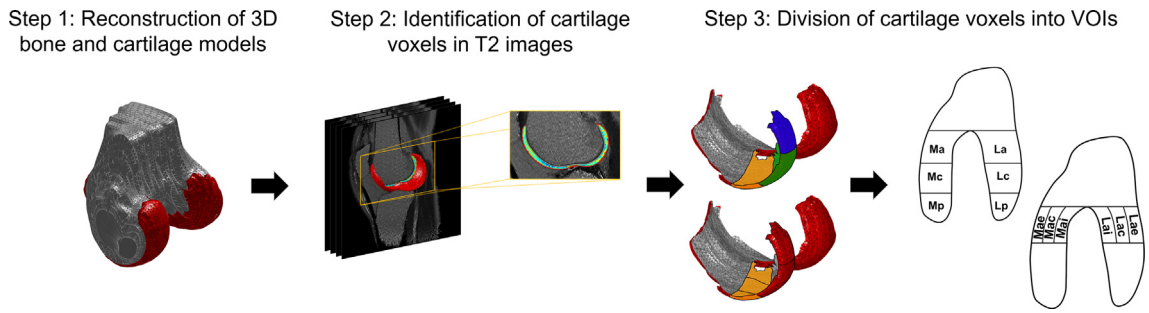


**Figure 1.** Illustration of the image analysis procedure. Step 1 consists of the reconstruction of bone and cartilage models by segmentation of the double echo steady state (DESS) morphology images. In Step 2, the bone and cartilage models are registered in the T2 images yielding the identification of the voxels belonging to cartilage (see Figure 2 for registration details). Step 3 consists of the separation of the cartilage voxels into volumes of interest (VOIs) and the calculation of the mean T2 relaxation time per VOI. La/Lc/Lp refer to lateral anterior/central/posterior VOIs, respectively. Lae/Lac/Lai refer to lateral anterior external/central/internal VOIs, respectively. Ma/Mc/Mp refer to medial anterior/central/posterior VOIs, respectively. Mae/Mac/Mai refer to medial anterior external/central/internal VOIs, respectively.

relaxation time images (Figure 2(c), (d)). The images corresponding to the first echo of the MSME acquisition were used for the registration because they provided the greatest contrast among tissues of all six echoes.

*2.3.3. Step 3: Measurement of mean T2 relaxation time per volume of interest*

The voxels identified as cartilage in the T2 relaxation time maps were divided into VOIs according to existing literature on morphological assessment of cartilage [22,24]. First, the cartilage covering the medial and lateral condyles was divided into anterior (load-bearing), central, and posterior VOIs (Figure 1). These VOIs were defined using the 3D bone and cartilage models following the VOIs template described by Pelletier et al. [22] and the separations among VOIs defined by Wirth and Eckstein [24]. The anterior load-bearing VOIs were further divided along the medial-lateral axis as per Wirth and Eckstein [24], resulting in anterior external, anterior central, and anterior internal VOIs on both condyles (Figure 1). These 12 VOIs were further divided into an additional 24 VOIs corresponding to the superficial and deep layers of cartilage, which were separated at half cartilage

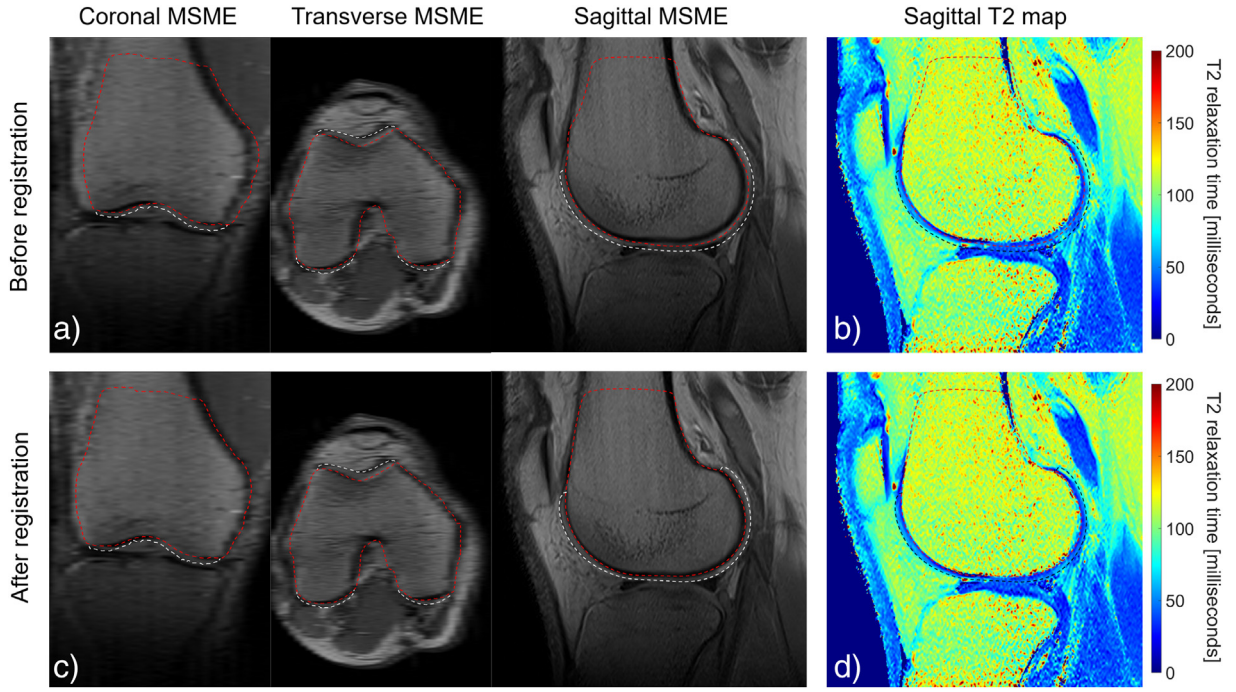


**Figure 2.** Example of manual registration of bone (red dashed line) and cartilage (white dashed line) models to fit the anatomy in the first echo images of the non-contrast multi-slice, multi-echo (MSME) T2 sequence (a and c) and in the corresponding T2 relaxation time maps (b and d). The first row corresponds to the initial registration made using DICOM header information and the second row to the final registration after manual tuning. While this figure includes four example images, it is important to note that the registration was performed considering all images available in the three anatomical planes. Specifically, coronal-, transverse-, and sagittal- plane MSME images (a and c) as well as sagittal-plane T2 relaxation time map images (b and d) were used to guide the manual registration. The sagittal plane images were interpolated to increase the through-plane resolution to 0.4 mm for improved visualization in the coronal- and transverse-plane MSME images.

thickness. A mean T2 relaxation time was calculated for each VOI by averaging the value of all cartilage voxels whose centroid belonged inside the VOI. According to prior literature [29], voxels with outlier values (i.e., negative relaxation times or relaxation times exceeding the median plus three times the interquartile range of the voxels in the VOI) were excluded from the mean calculation.

All processing in steps 1–3 was carried out with custom software implemented using Matlab (version R2014b, MathWorks, MA, USA).

### 2.4. Statistical analyses

#### 2.4.1. Method reliability

To assess the intra-rater reliability, the 10 knees were segmented and registered twice by a single operator on separate days. Results from both processes were first analyzed visually using Bland–Altman plots. The reliability was then evaluated using one-way random model intraclass correlation coefficients (ICCs) for each of the 36 VOIs. In addition, the standard error of measurement ($SE_m$) was calculated for each VOI as follows:

$$SE_m = SD\sqrt{1-ICC}, \quad (1)$$

where SD is the standard deviation of the mean T2 values within each VOI [30]. The $SE_m$ is an indicator of the precision of measuring mean T2 values over VOIs, thus providing important guidelines for the interpretation of T2 comparisons in future studies. The inter-rater reliability was assessed using the same procedure, but for two segmentations and registrations performed by different operators.

#### 2.4.2. Comparison of T2 relaxation times among VOIs

Repeated measures analysis of variance (ANOVA) and post hoc paired *t*-tests were used to compare the T2 values among the 12 full-depth VOIs. Additionally, paired *t*-tests were performed to compare the superficial and deep layers of these 12 VOIs. Significance level was set a priori at $\alpha = 0.05$, with Benjamini–Hochberg correction for multiple comparisons. All statistical calculations were performed using SPSS Statistics software (version 23, IBM, NY, USA).

## 3. Results

### 3.1. Method reliability

Bland–Altman plots indicated similar intra- and inter-rater reliability among all VOIs (examples shown in Appendix A. Supplementary data). According to Cicchetti's quality classifications [31], the intra-rater reliability for the 12 full-depth VOIs was 'excellent' (ICC between 0.75 and 0.99), and their inter-rater reliability was 'good' to 'excellent' (ICC between 0.66 and 0.94) (Table 1). The median intra-rater $SE_m$ was 0.99 ms, with a maximum value of 6.37 ms in the lateral anterior internal (Lai) VOI. In the inter-rater comparison, the median $SE_m$ was 1.90 ms, with a maximum value of 4.95 ms in the medial anterior internal (Mai) VOI.

**Table 1**
Intra- and inter-rater reliability for the 36 volumes of interest (VOIs).

| | | | Intra-rater | | | | | | Inter-rater | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Full-depth cartilage | | Superficial layer | | Deep layer | | Full-depth cartilage | | Superficial layer | | Deep layer | |
| VOI (abbreviation) | | | ICC | $SE_m$ (ms) | ICC | $SE_m$ (ms) | ICC | $SE_m$ (ms) | ICC | $SE_m$ (ms) | ICC | $SE_m$ (ms) | ICC | $SE_m$ (ms) |
| Lateral | | | | | | | | | | | | | | |
| Anterior | | (La) | 0.95 | 1.22 | 0.83 | 1.89 | 0.93 | 1.95 | 0.93 | 1.59 | 0.84 | 2.48 | 0.92 | 2.04 |
| | External | (Lae) | 0.95 | 0.66 | 0.93 | 0.82 | 0.97 | 0.56 | 0.81 | 1.37 | 0.80 | 1.50 | 0.82 | 1.54 |
| | Central | (Lac) | 0.89 | 2.56 | 0.77 | 3.09 | 0.90 | 3.58 | 0.66 | 4.39 | 0.52 | 5.04 | 0.76 | 0.93 |
| | Internal | (Lai) | 0.80 | 6.37 | 0.62 | 9.64 | 0.89 | 4.72 | 0.94 | 3.03 | 0.84 | 4.91 | 0.91 | 4.00 |
| Central | | (Lc) | 0.94 | 0.61 | 0.98 | 0.39 | 0.87 | 1.20 | 0.73 | 1.09 | 0.85 | 1.06 | 0.72 | 1.47 |
| Posterior | | (Lp) | 0.83 | 1.18 | 0.91 | 1.24 | 0.65 | 2.30 | 0.76 | 0.91 | 0.78 | 2.12 | 0.53 | 2.48 |
| Medial | | | | | | | | | | | | | | |
| Anterior | | (Ma) | 0.99 | 0.54 | 0.94 | 1.75 | 0.94 | 1.47 | 0.88 | 2.21 | 0.69 | 3.75 | 0.88 | 2.24 |
| | External | (Mae) | 0.92 | 1.76 | 0.88 | 2.38 | 0.61 | 3.62 | 0.66 | 3.25 | 0.61 | 4.17 | 0.66 | 3.12 |
| | Central | (Mac) | 0.98 | 0.86 | 0.91 | 2.06 | 0.97 | 1.18 | 0.81 | 2.90 | 0.54 | 4.46 | 0.79 | 3.63 |
| | Internal | (Mai) | 0.99 | 1.01 | 0.99 | 1.20 | 0.97 | 2.08 | 0.79 | 4.95 | 0.68 | 5.62 | 0.80 | 5.21 |
| Central | | (Mc) | 0.90 | 0.77 | 0.91 | 0.71 | 0.79 | 1.30 | 0.83 | 1.03 | 0.88 | 0.86 | 0.69 | 1.61 |
| Posterior | | (Mp) | 0.75 | 0.96 | 0.94 | 0.60 | 0.68 | 1.97 | 0.76 | 0.91 | 0.90 | 0.74 | 0.76 | 1.83 |

ICC, intraclass correlation; $SE_m$, standard error of measurement. La/Lc/Lp refer to lateral anterior/central/posterior VOIs, respectively. Lae/Lac/Lai refer to lateral anterior external/central/internal VOIs, respectively. Ma/Mc/Mp refer to medial anterior/central/posterior VOIs, respectively. Mae/Mac/Mai refer to medial anterior external/central/internal VOIs, respectively.

Intra-rater ICCs for the 24 superficial and deep cartilage layer VOIs were 'good' to 'excellent,' with coefficients ranging from 0.61 to 0.99. Inter-rater reliability for these superficial and deep layer VOIs was 'good' to 'excellent' for all VOIs except for the superficial lateral anterior central (Lac), superficial medial anterior central (Mac), and deep lateral posterior (Lp) VOIs, which reported 'fair' reliability (Table 1). The median intra- and inter-rater $SE_m$ of the 24 superficial and deep layer VOIs were 1.82 ms (maximum 9.64 ms in the Lai VOI) and 2.36 ms (maximum 5.62 ms in the Mai VOI), respectively.

### 3.2. Comparison of T2 relaxation times among VOIs

Repeated measures ANOVA indicated significant differences among mean T2 relaxation times in the medial and lateral anterior, central, and posterior full-depth VOIs ($P = .007$). Post hoc analysis comparing the three VOIs per condyle indicated longer T2 values in the central VOIs compared to the posterior VOIs on both the medial (Mc > Mp, $P < .001$) and lateral (Lc > Lp, $P < .01$) condyles (Table 2, Figure 3(a)). On the medial condyle, the T2 value in the anterior VOI was significantly longer than in the posterior VOI (Ma > Mp, $P = .03$).

Significant differences in T2 relaxation times were also found when comparing the six full-depth VOIs within the load-bearing anterior VOIs using repeated-measures ANOVA ($P < .001$). Post hoc analysis comparing the three VOIs per condyle indicated a general increase in T2 values from the external to the internal VOIs (Table 2, Figure 3(b)). Specifically, in both the medial and lateral compartments, T2 values were higher in the anterior internal VOIs compared to both the anterior central (Mai > Mac, $P < .001$; Lai > Lac $P < .01$) and anterior external (Mai > Mae, $P < .01$; Lai > Lae, $P < .001$) VOIs. Furthermore, the lateral anterior central region had higher T2 values compared with the lateral anterior external region (Lac>Lae, $P < .01$).

Significant differences were found between the superficial and deep cartilage layer T2 relaxation times. The superficial layer T2 values were higher than the deep layers in the medial and lateral anterior and central VOIs (Table 2, Figure 4(a)). Furthermore, in the six VOIs within the anterior VOI, all except for the Mai VOI exhibited higher superficial layer T2 values than in the deep layers (Table 2, Figure 4(b)).

## 4. Discussion

This study introduced a method of measuring mean T2 relaxation time in VOIs over the entire femoral condyles. Method assessment indicated 'good' to 'excellent' intra- and inter-rater reliability in all full-depth cartilage VOIs and in nearly 90% of the superficial and deep cartilage layer VOIs [31]. These reliability measures are comparable or superior to those of other methods previously tested, all of which used the MSME images for cartilage tissue segmentation [12,18,19]. As an example, for similar full-thickness VOIs spanning the femoral condyles, Surowiec and colleagues reported intra- and inter-rater ICCs ranging from 0.45 (lateral anterior VOI, inter-rater) to 0.95 (lateral central VOI, intra-rater) [19]. Furthermore, inter-subject variations (quantified by the standard deviation of T2 values in each VOI) of the presented method were an average of three times larger than the $SE_m$, and differences in mean T2 times between VOIs were larger than the corresponding $SE_m$. Together these results suggest that the method could reliably detect differences among knees and VOIs.

The presented method offers two notable improvements over previous techniques. First, cartilage tissue was identified using a standard morphological sequence (DESS), providing superior contrast between knee tissues than the often-used T2 MSME images [10,11,15,18,19]. Additionally, creating 3D bone and cartilage models using high-resolution morphological imaging and importing them into the T2 data space allowed for analysis of cartilage T2 relaxation time over the entire femoral condyles. This was not previously the case, as partial volume effects rendered it impossible to distinguish cartilage boundaries in some locations,

**Table 2**
Average and standard deviation (SD) T2 relaxation times over the 10 knees for the 36 volumes of interest (VOIs).

| | | | | Full-depth cartilage | | Superficial layer | | Deep layer | |
|---|---|---|---|---|---|---|---|---|---|
| VOI (abbreviation) | | | | Average | SD | Average | SD | Average | SD |
| Lateral | | | | | | | | | |
| | Anterior | | (La) | 50.0 | 5.5 | 53.2 | 4.8 | 46.5 | 7.9 |
| | | External | (Lae) | 41.6 | 2.8 | 44.7 | 3.2 | 38.2 | 3.1 |
| | | Central | (Lac) | 52.0 | 7.8 | 56.8 | 6.7 | 46.5 | 12.4 |
| | | Internal | (Lai) | 65.2 | 11.8 | 69.3 | 10.4 | 61.0 | 14.2 |
| | Central | | (Lc) | 49.4 | 2.6 | 52.0 | 2.8 | 46.8 | 3.5 |
| | Posterior | | (Lp) | 45.2 | 2.9 | 43.4 | 2.4 | 43.9 | 4.6 |
| Medial | | | | | | | | | |
| | Anterior | | (Ma) | 47.7 | 6.6 | 51.1 | 8.2 | 43.8 | 5.8 |
| | | External | (Mae) | 41.3 | 6.6 | 44.7 | 8.3 | 36.9 | 6.6 |
| | | Central | (Mac) | 44.7 | 6.6 | 50.0 | 8.1 | 37.8 | 6.5 |
| | | Internal | (Mai) | 59.0 | 11.8 | 58.1 | 11.4 | 59.9 | 12.5 |
| | Central | | (Mc) | 49.1 | 2.4 | 51.0 | 2.4 | 47.1 | 2.8 |
| | Posterior | | (Mp) | 42.3 | 2.2 | 43.4 | 2.4 | 41.1 | 4.8 |

Results from one processing completed by a single operator. Data are in ms. La/Lc/Lp refer to lateral anterior/central/posterior VOIs, respectively. Lae/Lac/Lai refer to lateral anterior external/central/internal VOIs, respectively. Ma/Mc/Mp refer to medial anterior/central/posterior VOIs, respectively. Mae/Mac/Mai refer to medial anterior external/central/internal VOIs, respectively.

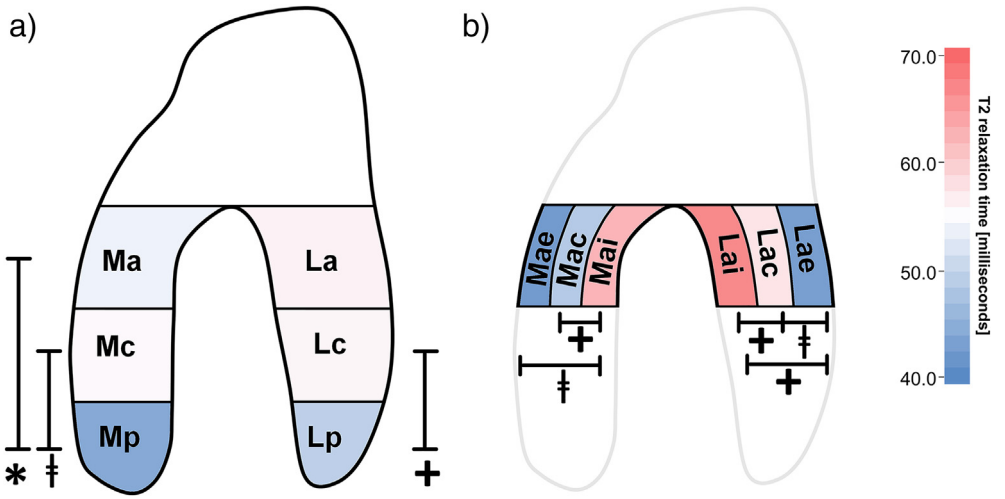


**Figure 3.** The average T2 relaxation times over the 10 knees are reported (color-coded) for the 12 full-depth VOIs. Significant differences between VOIs are marked as $^{*}P < .05$, $^{+}P < .01$), and $^{‡}P < .001$. La/Lc/Lp refer to lateral anterior/central/posterior VOIs, respectively. Lae/Lac/Lai refer to lateral anterior external/central/internal VOIs, respectively. Ma/Mc/Mp refer to medial anterior/central/posterior VOIs, respectively. Mae/Mac/Mai refer to medial anterior external/central/internal VOIs, respectively.

especially near the trochlear notch [18]. The possibility of evaluating cartilage compositional data over the entire femur could be a critical advantage as properties of healthy cartilage and alterations with OA vary spatially [18,20,22,23]. Additionally, this technique is not limited to use with the images or resolutions used in the current study. In fact, the morphological 3D models can be easily registered to higher-resolution T2 mapping sequences as they become available [32].

Second, the template of VOIs used to quantify T2 relaxation times was based on standard cartilage divisions that have been shown to detect changes in cartilage thickness with OA, suggesting their anatomical relevancy and potential for comprehensive cartilage compositional analyses [22,24]. Moreover, using the same cartilage divisions as those used in cartilage thickness research will allow for the comparison of current and future data, both morphological and compositional, thus potentially improving our understanding of healthy and OA cartilage properties.

Spatial variations in cartilage compositional properties, as measured by T2 relaxation time, were detected throughout the femoral cartilage in non-OA knees. Specifically, the posterior VOIs had shorter T2 values compared to the anterior and central VOIs. The reason for such patterns in healthy cartilage is not well-understood [18–20]. It has been shown that healthy cartilage adapts to the loads most commonly experienced, especially walking [33], with moderate cyclic loading in healthy cartilage causing an upregulation in chondrocyte collagen production [34]. Therefore, lower T2 relaxation time values, indicating a larger concentration of extracellular matrix components and greater tissue organization, would be expected in anterior and central

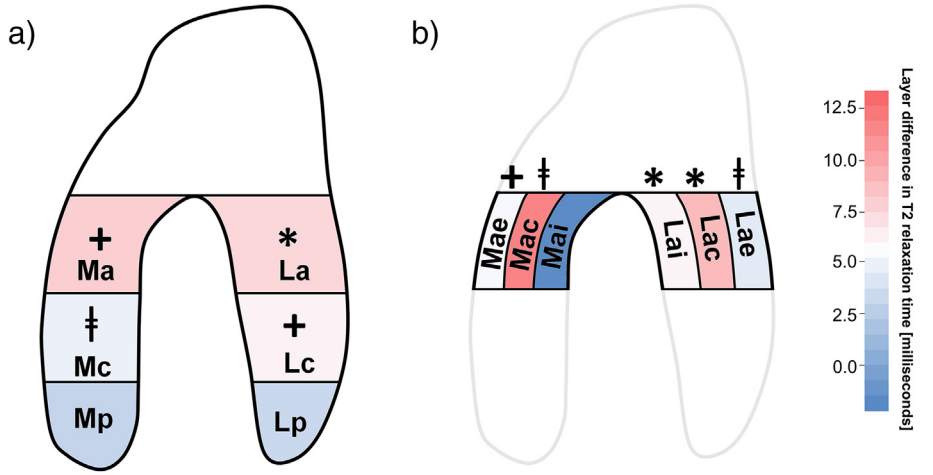


**Figure 4.** Color-coding indicates the difference (superficial-deep) between average cartilage layer T2 relaxation time per volume of interest (VOI). Significant differences between the superficial and deep layer T2 values of each VOI are marked as $^{*}P < .05$, $^{+}P < .01$, and $^{‡}P < .001$. La/Lc/Lp refer to lateral anterior/central/posterior VOIs, respectively. Lae/Lac/Lai refer to lateral anterior external/central/internal VOIs, respectively. Ma/Mc/Mp refer to medial anterior/central/posterior VOIs, respectively. Mae/Mac/Mai refer to medial anterior external/central/internal VOIs, respectively.

VOIs that sustain greater loads than posterior VOIs [6,35]. This apparent contradiction may be an indication that cartilage response to loading is heterogeneous, with compositional characteristics of posterior condylar cartilage being inherently different from the rest of the condyles [36].

Spatial variations were also observed within the load-bearing anterior VOIs, with increasing T2 values toward the intercondylar notch. The particular geometry of the femorotibial joint induces spatial variations in compressive loading, including relatively lower loads in the internal VOIs compared to the more external anterior VOIs [37]. Therefore, water content is likely higher and collagen concentration lower toward the intercondylar notch, resulting in longer T2 relaxation times [3–6,38].

Finally, comparing cartilage layers indicated longer T2 values in the superficial versus deep layers in the central and anterior VOIs, and in all but one of the six anterior VOIs. This finding of longer T2 relaxation times in the superficial layer extends our understanding of the locations where composition differs between superficial and deep cartilage [11,18]. These depth-related differences are likely due to the orientation of the extracellular matrix, which is columnar in the deep layer and parallel to the bone near the articulating surface [39].

The T2 values presented here may differ from some of those reported in the literature [13,40]. However, due to spatial variations in femoral T2 relaxation times, differences between studies can be caused by variations in VOI definitions. In fact, defining VOIs similar to those presented here have yielded comparable T2 relaxation times [15,19]. Additionally, magnetic resonance scanner equipment [41] and methods of calculating T2 relaxation times [42] are also known to affect T2 measurements. Therefore, it is not necessarily possible or advised to make direct comparisons across all T2 relaxation time studies.

The clinical implications of the presented T2 analysis method will be realized in its applications relating cartilage composition changes with potentially increased risks of cartilage structural loss or symptom development, thus conceivably providing a means of detecting early OA [2,7,43]. Furthermore, given that the results here suggest a specific spatial distribution of T2 times in healthy subjects, changes to this distribution could be used to detect subtle cartilage composition alterations. This may allow for a more sensitive assessment of treatments such as cartilage repair [44], ligament reconstruction [45], or high tibial osteotomy [46]. Furthermore, the proposed method facilitates the simultaneous analysis of cartilage thickness and composition, which will provide information regarding the temporality and location of cartilage changes more precisely in the progression of OA [2].

This study has some limitations, including the analysis of exclusively young, non-OA knees. While this population was selected to fulfill the present objectives, the reliability of the method and the spatial variations in T2 relaxation time motivate future research to characterize cartilage compositional properties, for example, in knee OA. Additionally, this study was limited to the analysis of femoral cartilage, and further work should extend it to the tibial cartilage. Finally, the measured T2 values may be influenced by the 'magic angle effect,' which influences the T2 value of cartilage depending on its orientation relative to the static magnetic field ($B_0$). The higher T2 values in the central VOIs may be at least partly due to this artifact, as some cartilage in this region is oriented at 55° from $B_0$ [47]. Thus, future studies should test for the influence of orientation of the imaged knees on spatial variation of cartilage T2 values using the presented technique [18].

In conclusion, this study presented a reliable method for analyzing T2 relaxation time of cartilage over the entire femoral condyles. The method included the registration of 3D bone and cartilage models from tissue segmentation performed on a morphological MRI sequence with a T2 mapping sequence. Using this technique, non-OA cartilage T2 values were found to vary along the condyles, within the load-bearing cartilage, and between the superficial and deep layers of cartilage, confirming the heterogeneity of cartilage composition and highlighting the promising potential of the method introduced in this study. Importantly, this tool to quantify the compositional properties of the entire femoral condylar cartilage could contribute to an improved understanding of knee OA pathophysiology along with techniques for identifying knees with an increased risk of OA development at a stage in which clinical interventions may be most effective.

## Acknowledgments

This work was partially supported by the Whitaker International Scholarship administered by the Institute of International Education (IIE). The authors thank Roberto Colotti for his help with data handling. B.M.J., P.O., and J.F. contributed equally to this work and should receive equal author recognition.

## Conflicts of interest

All of the authors declare that they have no financial or personal relationships that could inappropriately influence their work.

## Ethical statement

*Subject informed consent*

The presented study was approved by the Canton of Vaud ethics committee and all subjects were enrolled in the study after written informed consent.

*Ethics in publishing*

Each of the listed authors was involved in the conception, design, execution, interpretation, and/or manuscript preparation of the reported study. The authors also confirm that this is their original work and is being submitted only to The Knee journal for publication at this time. Furthermore, none of the authors declare any financial or personal relationships that could inappropriately influence this work.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.knee.2019.03.006.

## References


[1] Kean WF, Kean R, Buchanan WW. Osteoarthritis: symptoms, signs and source of pain. Inflammopharmacology 2004;12:3–31. https://doi.org/10.1163/156856004773121347.
[2] Oei EHGG, Van Tiel J, Robinson WH, Gold GE. Quantitative radiologic imaging techniques for articular cartilage composition: toward early diagnosis and development of disease-modifying therapeutics for osteoarthritis. Arthritis Care Res 2014;66:1129–41. https://doi.org/10.1002/acr.22316.
[3] Lüsse S, Claassen H, Gehrke T, Hassenpflug J, Schünke M, Heller M, et al. Evaluation of water content by spatially resolved transverse relaxation times of human articular cartilage. Magn Reson Imaging 2000;18:423–30. https://doi.org/10.1016/S0730-725X(99)00144-7.
[4] Fragonas E, Mlynárik V, Jellúš V, Micali F, Piras A, Toffanin R, et al. Correlation between biochemical composition and magnetic resonance appearance of articular cartilage. Osteoarthr Cartil 1998;6:24–32. https://doi.org/10.1053/joca.1997.0089.
[5] Liess C, Lüsse S, Karger N, Heller M, Glüer CG. Detection of changes in cartilage water content using MRI T2-mapping in vivo. Osteoarthr Cartil 2002;10:907–13. https://doi.org/10.1053/joca.2002.0847.
[6] Nieminen MT, Töyräs J, Rieppo J, Hakumäki JM, Silvennoinen J, Helminen HJ, et al. Quantitative MR microscopy of enzymatically degraded articular cartilage. Magn Reson Med 2000;43:676–81.
[7] Madry H, Kon E, Condello V, Peretti GM, Steinwachs M, Seil R, et al. Early osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc 2016;24:1753–62. https://doi.org/10.1007/s00167-016-4068-3.
[8] Hannila I, Lammentausta E, Tervonen O, Nieminen MT. The repeatability of T2 relaxation time measurement of human knee articular cartilage. MAGMA 2015;28:547–53. https://doi.org/10.1007/s10334-015-0494-3.
[9] Kato K, Arai Y, Ikoma K, Nakagawa S, Inoue H, Kan H, et al. Early postoperative cartilage evaluation by magnetic resonance imaging using T2 mapping after arthroscopic partial medial meniscectomy. Magn Reson Imaging 2015;33:1274–80. https://doi.org/10.1016/j.mri.2015.08.002.
[10] Hirose J, Nishioka H, Nakamura E, Oniki Y, Yamashita Y, Mizuta H. T1ρ and T2 mapping of the proximal tibiofibular joint in relation to aging and cartilage degeneration. Eur J Radiol 2012;81:2776–82. https://doi.org/10.1016/j.ejrad.2011.11.019.
[11] Smith HE, Mosher TJ, Dardzinski BJ, Collins BG, Collins CM, Yang QX, et al. Spatial variation in cartilage T2 of the knee. J Magn Reson Imaging 2001;14:50–5.
[12] Mosher TJ, Zhang Z, Reddy R, Boudhar S, Milestone BN, Morrison WB, et al. Knee articular cartilage damage in osteoarthritis: analysis of MR image biomarker reproducibility in ACRIN-PA 4001 multicenter trial. Radiology 2011;258:832–42. https://doi.org/10.1148/radiol.10101174.
[13] Soellner ST, Goldmann A, Muelheims D, Welsch GH, Pachowsky ML. Intraoperative validation of quantitative T2 mapping in patients with articular cartilage lesions of the knee. Osteoarthr Cartil 2017;25:1841–9. https://doi.org/10.1016/j.joca.2017.07.021.
[14] Dunn TC, Lu Y, Jin H, Ries MD, Majumdar S. T2 relaxation time of cartilage at MR imaging: comparison with severity of knee osteoarthritis. Radiology 2004;232:592–8. https://doi.org/10.1148/radiol.2322030976.
[15] Wirth W, Maschek S, Eckstein F. Sex- and age-dependence of region- and layer-specific knee cartilage composition (spin-spin-relaxation time) in healthy reference subjects. Ann Anat 2017;210:1–8. https://doi.org/10.1016/j.aanat.2016.10.010.
[16] Carballido-Gamio J, Link TM, Majumdar S. New techniques for cartilage magnetic resonance imaging relaxation time analysis: texture analysis of flattened cartilage and localized intra- and inter-subject comparisons. Magn Reson Med 2008;59:1472–7. https://doi.org/10.1002/mrm.21553.
[17] Carballido-Gamio J, Stahl R, Blumenkrantz G, Romero A, Majumdar S, Link TM. Spatial analysis of magnetic resonance T1rho and T2 relaxation times improves classification between subjects with and without osteoarthritis. Med Phys 2009;36:4059–67. https://doi.org/10.1118/1.3187228.
[18] Kaneko Y, Nozaki T, Yu H, Chang A, Kaneshiro K, Schwarzkopf R, et al. Normal T2 map profile of the entire femoral cartilage using an angle/layer-dependent approach. J Magn Reson Imaging 2015;42:1507–16. https://doi.org/10.1002/jmri.24936.
[19] Surowiec RK, Lucas EP, Fitzcharles EK, Petre BM, Dornan GJ, Giphart JE, et al. T2 values of articular cartilage in clinically relevant subregions of the asymptomatic knee. Knee Surg Sports Traumatol Arthrosc 2014;22:1404–14. https://doi.org/10.1007/s00167-013-2779-2.
[20] Shiomi T, Nishii T, Nakata K, Tamura S, Tanaka H, Yamazaki Y, et al. Three-dimensional topographical variation of femoral cartilage T2 in healthy volunteer knees. Skeletal Radiol 2013;42:363–70. https://doi.org/10.1007/s00256-012-1522-2.
[21] Erhart-Hledik JC, Favre J, Andriacchi TP. New insight in the relationship between regional patterns of knee cartilage thickness, osteoarthritis disease severity, and gait mechanics. J Biomech 2015;48:3868–75. https://doi.org/10.1016/j.jbiomech.2015.09.033.
[22] Pelletier J-P, Raynauld J-P, Berthiaume M-J, Abram F, Choquette D, Haraoui B, et al. Risk factors associated with the loss of cartilage volume on weight-bearing areas in knee osteoarthritis patients assessed by quantitative magnetic resonance imaging: a longitudinal study. Arthritis Res Ther 2007;9:R74. https://doi.org/10.1186/ar2272.
[23] Eckstein F, Yang M, Guermazi A, Roemer FW, Hudelmaier M, Picha K, et al. Reference values and Z-scores for subregional femorotibial cartilage thickness – results from a large population-based sample (Framingham) and comparison with the non-exposed osteoarthritis initiative reference cohort. Osteoarthr Cartil 2010;18:1275–83. https://doi.org/10.1016/j.joca.2010.07.010.
[24] Wirth W, Eckstein F. A technique for regional analysis of femorotibial cartilage thickness based on quantitative magnetic resonance imaging. IEEE Trans Med Imaging 2008;27:737–44. https://doi.org/10.1109/TMI.2007.907323.
[25] Omoumi P, Michoux N, Roemer FW, Thienpont E, Vande Berg BC. Cartilage thickness at the posterior medial femoral condyle is increased in femorotibial knee osteoarthritis: a cross-sectional CT arthrography study (part 2). Osteoarthr Cartil 2015;23:224–31. https://doi.org/10.1016/j.joca.2014.08.017.
[26] Omoumi P, Michoux N, Thienpont E, Roemer FW, Vande Berg BC. Anatomical distribution of areas of preserved cartilage in advanced femorotibial osteoarthritis using CT arthrography (part 1). Osteoarthr Cartil 2015;23:83–7. https://doi.org/10.1016/j.joca.2014.10.006.
[27] Li X, Benjamin Ma C, Link TM, Castillo DD, Blumenkrantz G, Lozano J, et al. In vivo T1ρ and T2 mapping of articular cartilage in osteoarthritis of the knee using 3 T MRI. Osteoarthr Cartil 2007;15:789–97. https://doi.org/10.1016/j.joca.2007.01.011.
[28] Koo S, Gold GE, Andriacchi TP. Considerations in measuring cartilage thickness using MRI: factors influencing reproducibility and accuracy. Osteoarthr Cartil 2005;13:782–9. https://doi.org/10.1016/j.joca.2005.04.013.
[29] Raya JG, Dietrich O, Horng A, Weber J, Reiser MF, Glaser C. T2 measurement in articular cartilage: impact of the fitting method on accuracy and precision at low SNR. Magn Reson Med 2010;63:181–93. https://doi.org/10.1002/mrm.22178.
[30] Weir JP. Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. J Strength Cond Res 2005;19:231–40.
[31] Cicchetti DV. Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. Psychol Assess 1994;6:284–90. https://doi.org/10.1037/1040-3590.6.4.284.
[32] Colotti R, Omoumi P, Bonanno G, Ledoux J-B, van Heeswijk RB. Isotropic three-dimensional $T_2$ mapping of knee cartilage: development and validation. J Magn Reson Imaging 2017:1–10. https://doi.org/10.1002/jmri.25755.
[33] Andriacchi TP, Favre J, Erhart-Hledik JC, Chu CR. A systems view of risk factors for knee osteoarthritis reveals insights into the pathogenesis of the disease. Ann Biomed Eng 2015;43:376–87. https://doi.org/10.1007/s10439-014-1117-2.
[34] Bleuel J, Zaucke F, Brüggemann GP, Niehoff A. Effects of cyclic tensile strain on chondrocyte metabolism: a systematic review. PLoS One 2015;10:1–25. https://doi.org/10.1371/journal.pone.0119816.
[35] Van Rossom S, Smith CR, Zevenbergen L, Thelen DG, Vanwanseele B, Van Assche D, et al. Knee cartilage thickness, T1ρ and T2 relaxation time are related to articular cartilage loading in healthy adults. PLoS One 2017;12:1–16. https://doi.org/10.1371/journal.pone.0170002.
[36] Bevill SL, Briant PL, Levenston ME, Andriacchi TP. Central and peripheral region tibial plateau chondrocytes respond differently to in vitro dynamic compression. Osteoarthr Cartil 2009;17:980–7. https://doi.org/10.1016/j.joca.2008.12.005.

[37] Shim VB, Besier TF, Lloyd DG, Mithraratne K, Fernandez JF. The influence and biomechanical role of cartilage split line pattern on tibiofemoral cartilage stress distribution during the stance phase of gait. Biomech Model Mechanobiol 2016;15:195–204. https://doi.org/10.1007/s10237-015-0668-y.
[38] Wayne JS, Kraft KA, Shields KJ, Yin C, Owen JR, Disler DG. MR imaging of normal and matrix-depleted cartilage: correlation with biomechanical function and biochemical composition. Radiology 2003;228:493–9. https://doi.org/10.1148/radiol.2282012012.
[39] Goodwin DW, Wadghiri YZ, Zhu H, Vinton CJ, Smith ED, Dunn JE. Macroscopic structure of articular cartilage of the tibial plateau: influence of a characteristic matrix architecture on MRI appearance. Am J Roentgenol 2004;182:311–8. https://doi.org/10.2214/ajr.182.2.1820311.
[40] Baum T, Joseph GB, Karampinos DC, Jungmann PM, Link TM, Bauer JS. Cartilage and meniscal T2 relaxation time as non-invasive biomarker for knee osteoarthritis and cartilage repair procedures. Osteoarthr Cartil 2013;21:1474–84. https://doi.org/10.1016/j.joca.2013.07.012.
[41] Balamoody S, Williams TG, Wolstenholme C, Waterton JC, Bowes M, Hodgson R, et al. Magnetic resonance transverse relaxation time T2 of knee cartilage in osteoarthritis at 3-T: a cross-sectional multicentre, multivendor reproducibility study. Skeletal Radiol 2013;42:511–20. https://doi.org/10.1007/s00256-012-1511-5.
[42] Koff MF, Amrami KK, Felmlee JP, Kaufman KR. Bias of cartilage T2 values related to method of calculation. Magn Reson Imaging 2008;26:1236–43. https://doi.org/10.1016/j.mri.2008.03.002.
[43] Dautry R, Bousson V, Manelfe J, Perozziello A, Boyer P, Loriaut P, et al. Correlation of MRI T2 mapping sequence with knee pain location in young patients with normal standard MRI. JBR-BTR 2014;97:11–6. https://doi.org/10.5334/jbr-btr.364.
[44] Guermazi A, Roemer FW, Alizai H, Winalski CS, Welsch G, Brittberg M, et al. State of the art: MR imaging after knee cartilage repair surgery. Radiology 2015;277:23–43. https://doi.org/10.1148/radiol.2015141146.
[45] Li X, Kuo D, Theologis A, Carballido-Gamio J, Stehling C, Link TM, et al. Cartilage in anterior cruciate ligament-reconstructed knees: MR imaging T1ρ and T2—initial experience with 1-year follow-up. Radiology 2011;258:505–14. https://doi.org/10.1148/radiol.10101006.
[46] Verschueren J, Meuffels DE, Bron EE, Klein S, Kleinrensink GJ, Verhaar JAN, et al. Possibility of quantitative T2-mapping MRI of cartilage near metal in high tibial osteotomy: a human cadaver study. J Orthop Res 2018;36:1206–12. https://doi.org/10.1002/jor.23729.
[47] Waldschmidt JG, Rilling RJ, Kajdacsy-Balla AA, Boynton MD, Erickson SJ. In vitro and in vivo MR imaging of hyaline cartilage: zonal anatomy, imaging pitfalls, and pathologic conditions. Radiographics 1997;17:1387–402. https://doi.org/10.1148/radiographics.17.6.9397453.