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Relationship between Knee Alignment and T1rho Values of Articular Cartilage and Menisci in Patients with Knee Osteoarthritis

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Abstract

Objective—To assess the relationship between knee alignment and subregional T1rho values of the femorotibial cartilage and menisci in patients with mild (Kellgren-Lawrence grade 1) to moderate (KL3) osteoarthritis (OA) at 3T.

Materials and methods—26 subjects with a clinical diagnosis of KL1-3 OA were included and subdivided into three subgroups: varus, valgus, and neutral. All subjects were evaluated on a 3T MR scanner. Mann-Whitney and Wilcoxon signed rank tests were performed to determine any statistically significant differences in subregional T1rho values of femorotibial cartilage and menisci among the three subgroups of KL1-3 OA patients.

Results—Medial femoral anterior cartilage subregion in varus group had significantly higher ($p < 0.05$) T1rho values than all cartilage subregions in valgus group. Medial tibial central cartilage subregion had significantly higher T1rho values ($p < 0.05$) than lateral tibial central cartilage

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Conflict of interest:

None.

subregion in varus group. The posterior horn of the medial meniscus in neutral group had significantly higher T1rho values ($p < 0.0029$) than all meniscus subregions in valgus group.

Conclusion—There exists some degree of association between knee alignment and subregional T1rho values of femorotibial cartilage and menisci in patients with clinical OA.

Keywords

knee alignment; osteoarthritis; MRI; meniscus; knee joint

Introduction

The prevalence of knee osteoarthritis (OA) in Americans over the age of 60 years old, already 13%, is expected to increase in the near future given the aging of the “Baby Boomers” as well as mounting problems with obesity (1, 2). It is well known that both systemic and local factors play a role in the pathogenesis of OA (2–7). Varus and valgus knee malalignment influences the distribution of load at the knee joint and has been shown to be a possible risk factor for OA development and progression (8). Although the medial compartment of the femorotibial joint is expected to bear approximately 60 – 80% of the compressive load in a knee in neutral alignment (9), this distribution is known to change significantly after even minimal alterations in lower limb alignment (10).

Using the MR quantitative morphologic imaging technique, Cicuttini and colleagues (11) demonstrated a relationship between varus deformity and femoral cartilage loss, with less evidence of this relationship in tibial cartilage. Eckstein and co-workers (12) found the medial-to-lateral ratio of femorotibial cartilage loss to be strongly affected by lower limb alignment. Correlations between thickness changes and knee alignment were stronger for the tibia than for the femur in the medial compartment (12). Friedrich and colleagues also assessed the relationship between T2 mapping of the femorotibial cartilage and knee alignment in patients with OA, and observed that the T2 values were significantly increased in the medial knee of patients with varus alignment (13).

T1rho (or T1 - T1 relaxation time in the rotating frame)-weighted MR imaging has recently been proposed as a promising alternative biomarker to existing conventional morphological MRI methods (14–16). Related techniques have been used to investigate the slow motion interactions between macromolecular protons and bulk water. Previous studies have shown that T1rho mapping is sensitive to biochemical changes in proteoglycan (PG) loss in hyaline cartilage (14, 15, 17, 18) and menisci (19, 20) with early OA. T1rho mapping technique may be a pre-structural indicator of OA (16, 19, 20).

The purpose of this study was to assess the relationship between lower limb alignment and quantitative subregional T1rho values of the articular cartilage and menisci in patients with a clinical diagnosis of knee OA.

Materials and methods

Local Institutional Review Board (IRB) approval and written, informed consent were obtained from all the recruited participants.

OA patients

26 radiographs and MRI exams of the knee in 26 patients with a clinical diagnosis of knee OA were retrospectively collected and studied. All the knee alignment patterns (varus,

valgus, and neutral) of all the recruited OA patients were degenerative. The demographics of the OA patients were listed in Table 1.

Radiographic analysis

MR imaging of the right femorotibial cartilage was performed in the symptomatic knees of 26 patients with femorotibial knee OA. Patients with OA were recruited from the local institution affiliated hospital for joint diseases knee OA cohort. Patients with OA had to fulfill the clinical criteria of the American College of Rheumatology (21) for the diagnosis of knee OA and show femorotibial Kellgren-Lawrence (KL) grade of 1–4 on standardized anteroposterior (AP) weight-bearing radiographs of the knee. KL scores were assigned as follows: 0 = no radiographic findings of OA, 1 = minute osteophytes of doubtful clinical significance, 2 = definite osteophytes with unimpaired joint space, 3 = definite osteophytes with moderate joint space narrowing, 4 = definite osteophytes with severe joint space narrowing and subchondral sclerosis (22).

Both anatomical alignment and severity of OA (Kellgren Lawrence criteria) (22) were assessed by a musculoskeletal fellowship trained radiologist with 6 years of experience (___). Exclusion criteria were any other form of arthritis or history of bilateral knee replacements.

Angles utilized for assessment of knee alignment were measured on a Siemens PACS workstation as shown in Fig. 1. The femoral anatomical axis was obtained by drawing a line from a point along the distal femoral articular surface midway between the femoral spines to a point along the distal femoral shaft 10 cm proximally, midway between the lateral and medial femoral cortices. The tibial anatomical axis was found by drawing a line from a point along the distal tibial articular surface midway between the tibial spines to a point along the proximal tibial shaft 10 cm distally, midway between the lateral and medial tibial cortices (13). The medial angle of intersection of the femoral and tibial anatomical axes was measured. Knee alignment was considered neutral if the medial angle measured between 182° – 184° , valgus if $>184^{\circ}$, and varus if $<182^{\circ}$ (23).

MR imaging and analysis

All MRI examinations were performed on a 3T clinical MR scanner (Magnetom Tim Trio, Siemens Medical Solutions, Erlangen, Germany). An 18-cm diameter, 8-channel transmit-receive phased-array (PA) knee coil was employed for the imaging measurements.

The morphology of the cartilage was assessed by acquiring routine clinical sequences which included sagittal proton density (PD)-weighted without fat saturation and axial and coronal PD-weighted fast spin echo (FSE) fat-saturated images used for Whole-Organ MR Imaging Score (WORMS) grading.

For 3D-T1rho Imaging, 3D T1rho-weighted images with parallel imaging (acceleration factor [AF] = 2) were acquired using the GRE sequence based on the spin-lock technique.

The acquisition parameters of all MR imaging sequence were listed in Table 2.

For quantitative T1rho assessment, all the MR images were analyzed based on the subregional meniscus and femorotibial cartilage in both lateral and medial compartments. Twelve subregions for femorotibial cartilage and six subregions for the meniscus were defined in each subject: lateral femoral anterior (LFa), lateral femoral central (LFC), lateral femoral posterior (LFp), medial femoral anterior (MFA), medial femoral central (MFC), medial femoral posterior (MFP), lateral tibial anterior (LTa), lateral tibial central (LTC), lateral tibial posterior (LTP), medial tibial anterior (MTa), medial tibial central (MTC),

medial tibial posterior (MTp) for femorotibial cartilage assessment, and lateral anterior (La), lateral central (Lc) [lateral-side body segment], lateral posterior (Lp), medial anterior (Ma), medial central (Mc) [medial-side body segment], medial posterior (Mp) for meniscus assessment just similar to those defined in the literature (24–26) and in Fig. 2 for the subregional demarcation of the meniscus and femorotibial cartilage.

The in-house developed routines in MATLAB (version 7.1; The Mathworks, Natick, MA, USA) and C++ were used for offline processing of the acquired MR images including cartilage and menisci segmentation, and calculation of regional T1rho values. The signal intensities of the T1rho-weighted images were fitted on a pixel by pixel basis using a linear least-squares method as previously described (27):

$$S(x) = A(x) * \frac{e^{-TSL/T1\rho(x)} \left(1 - e^{-(TR-TSL)/T1(x)} \right)}{1 - e^{-TSL/T1\rho(x)} e^{-(TR-TSL)/T1(x)} \cos \alpha} \sin \alpha \quad (1)$$

where x is the pixel coordinate, α is the flip angle, TR is the repetition time, $A(x)$ is the amplitude of the signal, $T1(x)$ is the spin-lattice relaxation time of the tissue to which the pixel belongs. Eq. 1 represents a decay when it is considered as a function of TSL. It is possible to estimate T1rho (x) by fitting the curve represented by Eq. 1 to the intensities of the pixel in images acquired with different TSL values. For each 3D data set which consists of the 3D scans of the same subject with 4 different TSL values (4 3D images), each pixel in the regions of interest (ROIs) was fitted to the Eq. 1 in least-squared (LS) sense.

The ROIs used in this study consisted of the above-defined subregions of femorotibial cartilage and meniscus. All ROIs were constructed by segmenting these anatomical structures manually (by $__$) at each slice of the 3D data. For the segmentation, the 3D image acquired with TSL = 2 ms was used since it has the highest signal-to-noise ratio (SNR) compared to others acquired with longer TSL values (Fig. 2).

The custom-build MATLAB routine ultimately yielded colour-coded T1rho maps, in which the manually segmented cartilage and meniscus ROIs were overlaid on the shortest spin-lock length (TSL = 2 ms) images.

Statistical analysis

Statistical analysis was performed using a SAS version 9.0 (SAS Institute, Cary, NC). As non-parametric analyses were conducted, results are summarized as mean $\pm$ SD and median $\pm$ inter-quartile range (IQR) (not listed).

The patients were divided into three subject groups with respect to knee alignment as varus, valgus, or neutral. The Mann-Whitney test was utilized to obtain the p values comparing T1rho measurements in each of the 12 cartilage and 6 meniscus subregions for each pairing of subject groups (valgus vs. varus, valgus vs. neutral, and varus vs. neutral). The Wilcoxon signed rank test was performed to calculate p values when comparing mean T1rho values for the medial and lateral cartilage compartments (i.e. MFa vs. LFa) in each subject group (varus, valgus, neutral). The Wilcoxon signed rank test was also used to calculate p values when comparing mean T1rho values for the medial and lateral meniscal segments (i.e. lateral meniscus anterior horn vs. medial meniscus anterior horn) in each subject group (varus, valgus, and neutral).

Lastly, the Wilcoxon signed rank test was performed to calculate p values when comparing the mean T1rho values for the articular cartilage along both the femoral and tibial surfaces to the mean T1rho values for the anterior horn, central subregion (body segment), and posterior horn of menisci, stratified by compartment (lateral and medial) and subject knee alignment

group (varus, valgus, and neutral). All reported p values were considered statistically significant when $p < 0.05$.

Results

Regarding knee alignment, 6 patients were varus, 7 patients were valgus, and 13 patients were neutral, respectively. The mean knee alignment angle (mean $\pm$ SD) for varus, valgus, and neutral groups were $177.7 \pm 2.2^\circ$, $187.2 \pm 2.2^\circ$, and $183 \pm 0.8^\circ$, respectively. The percentage coefficient of variation (CV %) of the knee alignment angle measurement for varus, valgus, and neutral groups were 1.24, 1.18, and 0.44, respectively. As for KL classification, 1 patient had KL score 1, 17 patients had score 2, and 8 patients had score 3, respectively.

Representative T1rho maps of cartilage on the lateral (a) and medial (b) side, and T1rho maps of meniscus on the lateral (c, e) and medial (d, f) side obtained from the same patient as in Fig. 1. were displayed in Fig. 3. The color bar scale on the right shows the distribution of T1rho values. Fig. 4 showed the bar chart of T1rho values within each cartilage and meniscus subregions for varus, valgus, and neutral alignment subgroups, respectively.

When comparisons were made between the same cartilage subregions among the varus, valgus, and neutral subgroups (Table 3), the following findings were identified statistically significant: The varus and neutral groups had significantly higher T1rho values (64 ± 14 ms and 58 ± 10 ms, respectively) within the LTa cartilage subregion compared to the valgus group (53 ± 2 ms) with $p = 0.0016$, and $p = 0.0479$, respectively. The varus group (Fig. 4) also had significantly higher T1rho values (69 ± 9 ms) at the MFa subregion than the valgus group (59 ± 10 ms) with $p = 0.0482$. The neutral group had significantly higher T1rho values (49 ± 11 ms) at the MTa subregion than the valgus group (43 ± 6 ms) with $p = 0.0144$. In addition, the neutral group also had significantly higher T1rho values (41 ± 9 ms) at the Mp meniscus subregion than the valgus group (31 ± 6 ms) with $p = 0.0029$ (Fig. 4 and Table 3).

When comparisons were made between the same cartilage subregions of different compartments (i.e. MFa vs. LFa) within each group (varus, valgus, and neutral) (Fig. 4 and Table 4), the following findings were identified statistically significant: The varus group had significantly higher T1rho values at LTa (64 ± 8 ms) than MTa (52 ± 11 ms) with $p = 0.0484$. The varus group also had significantly higher T1rho values at MTc (59 ± 8 ms) than LTc (46 ± 7 ms) with $p = 0.0158$. The valgus group had significantly higher T1rho values (53 ± 2 ms) at LTa than MTa (43 ± 6 ms) with $p < 0.0002$. The neutral group had significantly higher T1rho values (58 ± 12 ms) at MTc than LTc (50 ± 8 ms) with $p < 0.0459$.

When comparisons were made between the same meniscal regions among the varus, valgus, and neutral subgroups, the only significant finding was that the neutral subgroup had significantly higher T1rho values (41 ± 9 ms) at the posterior horn of the medial meniscus than the valgus subgroup (31 ± 6 ms) with $p = 0.0029$ (Fig. 4 and Table 4).

When comparisons were made between the same meniscal regions in the medial and lateral compartments within each subgroup (varus, valgus, and neutral), the only significant finding was that the neutral subgroup had significantly higher T1rho values at the central subregion (36 ± 7 ms) and posterior horn (41 ± 9 ms) of the medial meniscus compared to the lateral meniscus (Fig. 4 and Table 4).

There existed statistically significant differences ($p < 0.05$) in correlation of T1rho values between menisci and femorotibial cartilage stratified by knee joint compartment except that of T1rho values between medial femorotibial cartilage and central meniscus subregion in

varus subgroup and between lateral femorotibial cartilage and central meniscus subregion in valgus subgroup ($p > 0.05$) (Fig. 4 and Table 5).

Discussion

In this study, T1rho mapping technique for the first time was used to perform quantitative analyses and evaluation of the possible correlation relationship between knee joint alignment and T1rho values for cartilage and menisci in patients with clinical knee OA of KL1–3.

OA, although multi-factorial in origin, is felt to result primarily from mechanical factors acting within the context of systemic susceptibility. A systematic review performed by Tamanas et al. (28, 29) found limited evidence for a relationship between knee alignment and the incidence of knee OA. However, they did find strong evidence for knee malalignment as an independent risk factor for progression of knee OA on radiographs and MR imaging.

Varus positioning causes the axial load vector to pass more medially during ambulation. This results in increased loads and accelerated OA within the medial compartment (9). Our findings support this concept, with significantly higher T1rho values at the MTa and MTc in patients with varus malignment (Fig. 4 and Table 4). Eckstein et al. (12) also detected a significant reduction in cartilage thickness in the medial tibia in patients with varus alignment when comparison was made with neutral alignment. Friedrich et al. (13) also found similar results, as patients with varus alignment had significantly higher T2 values of cartilage of the medial femorotibial compartment than patients with valgus alignment. By the same logic, valgus malalignment has been shown to predispose to the progression of degenerative changes within the lateral compartment of the knee (8). Eckstein et al.'s (12) findings support this theory as they detected a significant loss of cartilage thickness in the lateral tibia of patients with valgus alignment when comparison was made with neutral knees. Our results also partially support this theory with significantly higher T1rho values at the LTa compared to the MTa in the valgus group. However, we noticed that patients with OA and neutral or varus malalignment had significantly higher T1rho values at the LTa when compared to the valgus group. We believe that this result is probably due to the higher frequency of advanced degenerative disease within the varus and neutral groups compared to the valgus group.

It is also well known that the medial femorotibial compartment bears 60–80% of the compressive load in a knee in neutral alignment (9). Our results would support this contention with significantly higher overall T1rho values within the central subregion and posterior horn of the medial meniscus and within the cartilage at the MTc in patients with OA and neutral alignment. This would seem to imply an association between degeneration of articular cartilage and menisci which may be similarly affected by changes in joint alignment. Of note, significantly higher T1rho values for LTa compared to MTa was found in the varus group which is contrary to what was expected (Fig. 4 and Table 4). This inconsistency may indicate that the development and progression of OA may be multi-factorial and complicated, and knee malalignment may be only one possible risk factor of the degeneration of articular cartilage. Much and further work remains warranted to explore the etiology and pathogenesis of OA.

This study definitely has several limitations, including a relatively small study population, lack of correlation between T1rho values, imaging scores for OA and body mass index, and lack of full-limb radiographs for accurate angle measurement of mechanical alignment. However, a study from Kraus et al. demonstrated a strong correlation between data obtained from full-limb measures of the mechanical axis and short-film measures of the anatomic axis

(30). Additionally, the acquisition and measurement of the mechanical axis is technically difficult and does not avoid pelvic radiation, as opposed to the short-film measurement technique.

Conclusion

This study implied some degree of correlation relationship between femorotibial cartilage degeneration as measured utilizing the T1rho mapping technique and knee alignment. T1rho values were significantly higher within femorotibial cartilage at the MTa and MTc in OA patients with varus alignment supporting the connection that varus alignment results in increased load forces in the medial compartment and possibly accelerated cartilage degeneration. Correlation relationships were also noted between the distribution of T1rho values in the meniscal segments in the medial and lateral compartments with respect to knee alignment. Significantly higher T1rho values were identified within posterior horn and central subregion of medial meniscus as well as femorotibial cartilage at the MTc in OA patients with neutral knee alignment. These findings may be supportive of the multifactorial etiology of OA and provide useful information regarding the possible risk factors of development and progression of knee OA.

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Fig. 1. Representative weight-bearing anteroposterior (AP) radiograph of both knees with alignment measurement made at the right knee obtained from a 63-year old male patient with clinical symptoms of OA and KL score of 2. The measured angle is 181° (varus alignment).

Fig. 2.

Representative sagittal fat-saturated T1rho-weighted 3D gradient-echo image with time of spin-lock (TSL) = 2 ms illustrating how the cartilage and meniscus subregions in the lateral [Fig. 2(a, c)] and medial [Fig. 2(b, d)] compartments were defined. White lines demarcate the anterior (a), central (c), and posterior (p) subregions of the lateral and medial femoral condyle (LF and MF) and lateral tibial and medial plateau (LT and MT) of the cartilage. White arrowheads mark the location of the meniscus body segment (central) in the lateral (Lc) [Fig. 2(c)] and medial (Mc) [Fig. 2(d)] compartments, respectively obtained from an OA patient of KL2 with varus alignment.

Fig. 3.
Representative T1rho maps of cartilage and meniscus from the same patient as in Fig. 1. T1rho maps of cartilage on the lateral (a) and medial (b) side, and T1rho maps of meniscus on the lateral (c, e) and medial (d, f) side. The color bar scale on the right shows the distribution of T1rho values.

Fig. 4.

The bar chart of T1rho values within each cartilage and meniscus subregions for varus, valgus, and neutral alignment subgroups, respectively.

Table 1

Characteristics of the Study Population

Patients Group and Characteristics	Varus *	Valgus	Neutral
All patients			
No. of patients	6	7	13
Age (yrs)	69.8±7.0	61.1±11.8	66.8±11.0
BMI (kg/m ²)	25.6±3.4	27.4 ± 3.5	25.7 ± 3.9
Total WORMS	20.6±19.0	20.6±13.7	20.3±15.0
Female patients			
No. of patients	0	5	8
Age (yrs)	0	59.6 ±14.0	67.6±10.8
Age range (yrs)	0	40 – 78	53 – 89
Male patients			
No. of patients	6	2	5
Age (yrs)	69.8±7.0	65 ±2.8	65.4±12.5
Age range (yrs)	60 – 78	63 – 67	46 – 80

Note: WORMS = Whole-Organ MR Imaging Score.

BMI = Body Mass Index.

* There were significant differences ($p < 0.05$) in patients' gender between varus and valgus subgroups ($p = 0.0045$), varus and neutral subgroups ($p = 0.0093$).

Table 2**MR Imaging Sequence Parameters**

Imaging Parameters	2D FSE	2D FSE	2D FSE	3D-T1rho
Weighting	PD	PD	PD	GRE
Plane	Sagittal	Axial	Coronal	Sagittal
Fat sat	No	Yes	Yes	Yes
Matrix	512 × 512	512 × 512	512 × 512	256 × 128
No. of slices	35	35	35	30
FOV (mm)	100	100	100	150
Slice thickness (mm)	2.5	2.5	2.5	3
Flip angle (°)	90	90	90	25
TE (ms)	19	19	19	2.04
TR (ms)	3030	3240	3240	175
BW (Hz / pixel)	255	255	255	260
In-plane spatial resolution (mm)	0.19 × 0.19	0.19 × 0.19	0.19 × 0.19	0.59 × 0.59
Echo train length	5	5	5	1
NEX	1	1	1	1
duration of each 90° pulse (us)	1536	1536	1536	200
Acceleration factor	–	–	–	2
Spin-lock frequency (Hz)	–	–	–	300
Time of spin-lock (TSL) [ms]	–	–	–	2/10/20/30
Acquisition time (TA)	2 minutes 4 seconds	2 minutes 4 seconds	2 minutes 5 seconds	5 minutes 31 seconds / TSL

Table 3

p values of Mann-Whitney (MW) test performed to compare pairs of subjects' knee alignment groups in terms of T1rho values of cartilage and meniscus subregions

cartilage/meniscus subregions	varus vs. valgus	varus vs. neutral	valgus vs. neutral
LFa	0.1167	0.3293	0.3159
LFc	0.2443	0.5483	0.6343
LFp	0.4572	0.433	0.9186
LTa	<i>0.0016</i>	0.1984	<i>0.0479</i>
LTc	0.0725	0.3991	0.2013
LTp	0.6788	0.9432	0.5691
MFa	<i>0.0482</i>	0.1615	0.4111
MFc	0.4258	0.8365	0.4884
MFp	0.1247	0.7631	0.1657
MTa	0.0833	0.882	<i>0.0144</i>
MTc	0.1336	0.486	0.4022
MTp	0.3406	0.8706	0.258
La	0.2723	0.0797	0.5658
Lc	0.6522	0.4092	0.8381
Lp	0.0969	0.2432	0.3906
Ma	0.831	0.1065	0.0851
Mc	0.6776	0.754	0.3695
Mp	0.1103	0.5409	<i>0.0029</i>

Note: $p < 0.05$ – statistically significant difference (bold italic) vs. - versus

p values of Wilcoxon signed rank test performed to compare lateral and medial cartilage and meniscus compartments in terms of T1rho values among subjects' knee alignment groups

Table 4

cartilage/meniscus subregions		varus	valgus	neutral
cartilage	anterior	0.8816	0.5043	0.6005
	Central	0.8816	0.9521	0.5
	posterior	0.7653	0.6727	0.3273
	anterior	0.0484	0.0002	0.0595
	Central	0.0158	0.6727	0.0459
	posterior	0.8816	0.9521	0.7843
meniscus	Anterior	0.9988	0.1902	0.7043
	Central	0.2316	0.9988	0.018
	Posterior	0.1119	0.2392	0.026

Note: *p* < 0.05 – statistically significant difference (bold italic)

p values of Wilcoxon signed rank test performed to compare T1rho values of femorotibial cartilage to T1rho values of anterior, central, posterior meniscus subregions stratified by compartment (lateral and medial) and subjects' knee alignment group (varus, valgus, and neutral)

Table 5

knee alignment group	cartilage		meniscus		
	compartment	bone	anterior	central	posterior
Varus	lateral	femur	0.0313	0.0313	0.0313
		tibia	0.0313	0.0313	0.0313
	medial	femur	0.0313	0.0625	0.0313
		tibia	0.0313	0.0625	0.0313
valgus	lateral	femur	0.0156	0.0625	0.0156
		tibia	0.0156	0.0625	0.0313
	medial	femur	0.0156	0.0313	0.0156
		tibia	0.0156	0.0313	0.0156
neutral	lateral	femur	0.0005	0.0005	0.0007
		tibia	0.0005	0.0005	0.0005
	medial	femur	0.0024	0.001	0.0034
		tibia	0.0215	0.001	0.0134

Note: *p* < 0.05 – statistically significant difference (bold italic)