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Does joint alignment affect the T2 values of cartilage in patients with knee osteoarthritis?

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Abstract

Objective—To assess the relationship between T2 values of femorotibial cartilage and knee alignment in patients with clinical symptoms of medial osteoarthritis (OA).

Methods—Twenty-four patients (mean age $\pm$ standard deviation, 62.5 ± 9.9 years) with clinical symptoms of medial knee OA, 12 with varus and 12 with valgus alignment of the femorotibial joint, were investigated on 3T MR using a 2D multi-echo spin echo (MESE) sequence for T2 mapping. Analysis of covariance, Spearman correlation coefficients, exact Mann-Whitney tests, and Fisher's exact tests were used for statistical analysis.

Results—Overall the T2 values of cartilage in the medial compartment (median $\pm$ interquartile-range, 49.44 ± 6.58) were significantly higher ($P=0.0043$) than those in the lateral compartment (47.15 ± 6.87). Patients with varus alignment (50.83 ± 6.30 ms) had significantly higher T2 values of cartilage ($P<0.0001$) than patients with valgus alignment (46.20 ± 6.00 ms). No statistically significant association between the T2 values of cartilage (in either location) and the Kellgren Lawrence score was found in the varus or in the valgus group.

Conclusion—T2 measurements were increased in medial knee OA patients with varus alignment, adding support to the theory of an association of OA and joint alignment.

Keywords

MRI; Cartilage; T2 mapping; Alignment; Osteoarthritis

Introduction

Malalignment of the lower leg has been shown to influence the distribution of load at the knee [1]. Although the medial compartment of the femorotibial joint bears 60–80% of the

compressive loads in a neutrally aligned knee [2], minor alterations in knee alignment significantly alter this load distribution [1]. The increase in compartment loading is thought to increase stress on articular cartilage and other joint components, subsequently leading to degenerative changes [3].

There is evidence that knee malalignment is an independent risk factor for radiographic progression of osteoarthritis (OA) as well as findings on MRI in patients with knee OA. This being said there is surprisingly sparse evidence of an association between knee malalignment and incident knee OA, especially prestructural OA [3].

Quantitative T2 mapping provides information about the interaction of water molecules and the collagen network within the articular cartilage [4]. This technique is well accepted as a prestructural indicator of OA [5–7]. It has been shown that alterations in T2 values correlate with the changes in water content and changes in collagen structure, orientation and organisation that are associated with changes in hyaline cartilage [6, 8, 9].

The purpose of this study was to assess the relationship between T2 values of femorotibial cartilage and knee alignment in patients with clinical symptoms of medial knee OA.

Materials and methods

Study population

Institutional review board approval and written, informed consent were procured. Body height and weight for the calculation of the body mass index (BMI) were obtained from all subjects. Patients with a BMI greater than 24.9 were classified as “overweight”; patients with a BMI of more than 29.9 were classified as “obese”.

One side in each of the 24 patients with knee OA was prospectively investigated.

Only patients with clinical symptoms of OA (pain, stiffness or crepitus) were included in the study. Moreover patients had to be from 50 to 90 years old, and must have had AP, weight-bearing, short knee radiographs performed within 1 month prior to the study MRI. Joint space width (JSW) was measured along a vertical line drawn from the midpoint of the femoral condyle to the tibial plateau, in both the medial and lateral compartments. JSW was defined as the interbone distance between the distal convex margin of the femoral condyle and the floor of the tibial plateau [10]. The JSW of the medial compartment was subtracted from the JSW of the lateral compartment. Those patients with a negative number as a result of this subtraction were excluded from the study. Subjects with congenital disorders, primary or secondary tumours, infections, inflammatory arthropathies, fractures, or previous knee surgery as well as subjects with known contraindications for MRI were excluded from the study as well.

Four patients who were included in the study were classified as Kellgren Lawrence (KL) score 1, five as KL score 2, eight as KL score 3 and seven as KL score 4 [11]. All the patients had been referred for x-ray examinations by their rheumatologists based on clinical symptoms of OA.

The mean age of the study population was 62.5 ± 9.9 years; 11 were male (mean age, 62.8 ± 6.2), and 13 female (mean age, 62.3 ± 12.4).

MR imaging

MRI was performed on 3.0T MRI (Magnetom Tim Trio, Siemens Medical Solutions, Erlangen, Germany) using an 18-cm diameter, 8-channel transmit-receive phased-array (PA) knee coil.

The following imaging sequence was employed: a sagittal 2D multi-echo spin echo (MESE) sequence with fat saturation and with a repetition time (TR) of 4,000 ms; echo times (TE) of 16.5, 33, 49.5, 66 and 82.5 ms; a field of view (FOV) of 15×15 cm; a matrix of 256×128 (interpolated to 256×256); a bandwidth of 130 Hz/pixel; and a slice thickness of 1.5 mm (interslice gap=100%). The acquisition time was 8 min and 30 s.

Image analysis

KL scores and assessment of anatomical alignment angles were performed by an experienced observer (M.E.S.; 20 years of subspecialty experience).

For the assessment of anatomical alignment, angles were measured on AP, weight-bearing, short knee radiographs on a Siemens PACS workstation in the following manner: A dot was placed at the midpoint of the tibial spines. The femoral anatomical axis was then found by drawing a line from the midpoint of the tibial spines to a point 10 cm above the tibial spines, midway between the medial and lateral femoral cortical bone surfaces. The tibial anatomical axis was found by drawing a line from the midpoint of the tibial spines to a point 10 cm below the tibial spines, midway between the medial and lateral cortical bone surfaces (Figs. 1a, 2a). The medial angle of the intersection of the axes was then measured, with measurements recorded as either >180° or <180° depending on valgus or varus malalignment [12]. In addition, the joint space width was assessed using digital callipers measuring the interbone distance at the narrowest point perceived, both in the medial and lateral compartment [13].

For the evaluation of the femorotibial cartilage, four regions were defined: the medial femoral condyle (MFC), the lateral femoral condyle (LFC), the medial tibial plateau (MTP) and the lateral tibial plateau (LTP). The femoral trochlea was considered part of the MFC. The boundary between MFC and LFC was defined by a plane aligned with the lateral wall of the femoral notch [14]. A MATLAB (version 7.1; The Mathworks, Natick, MA, USA) routine developed in-house was used for offline processing of the acquired MR images including cartilage segmentation and calculation of regional T2 values. The signal intensities of the T2-weighted images were fitted on a pixel by pixel basis using a linear least-squares method

$$\ln \left| \frac{S(TE)}{S_0} \right| = \left(\frac{-TE}{T_2} \right) + C.$$

where S(TE) is the measured signal intensity of the image at a particular echo time (TE), S₀ is the signal intensity at shortest TE and C is an intercept (i.e. point where the graph of a function or relation intercepts the axis of the coordinate system). Stimulated echoes that are created by imperfect refocusing pulses in the MESE sequence lead to overestimation of the T2 values; to minimise this error, the first echo of the MESE sequence was excluded from the T2 calculation.

For the calculation of the T2 values, the image acquired with the shortest TE was used to estimate the relative spin density. Once this value was known, the natural logarithm of the MESE images could be calculated, which reduced the relation between the observed signal intensities and the T2 values to a linear dependence. Then a linear curve fit in least-squares

(LS) sense was applied to the transformed data on a pixel by pixel basis, and the negative of the reciprocal of the slope gave the T2 values. Similarly, for the regional analysis of the T2 values, regions of interest (ROI) were manually drawn for the MFC, LFC, MTP, and LTP using a custom-built MATLAB routine. The custom-built MATLAB routine ultimately yielded colour-coded T2 maps, in which the manually segmented cartilage ROIs were overlaid on the shortest echo time (TE=16.5 ms) images.

The MESE images were assessed by an experienced musculoskeletal radiologist (M.E.S.) for the presence of meniscal and/or ACL tears. In addition, the images were evaluated for the presence of a meniscal extrusion. Thus, measurements were performed first drawing a vertical line intersecting the peripheral margin of the tibial plateau at the point of transition from horizontal to vertical; the length of another line extending from the first line to the outer margin of the meniscus was measured to assess meniscal extrusion. A measurement of 3 mm was defined as an extrusion of the meniscus [15, 16]. The margin was considered to be the edge of the tibial plateau independent of the presence of osteophytes.

Statistical analysis

Statistical analysis was performed using SAS version 9.0 (SAS Institute, Cary, NC). As non-parametric analyses were conducted, results are summarised as median $\pm$ inter-quartile (IQ) range.

Analysis of covariance (ANCOVA) based on ranks was used to compare the T2 values of the patients with varus alignment with those of the patients with valgus alignment, while adjusting for the potential confounding effects of age, gender, BMI, KL score and the presence of ACL or meniscal tears, medial and lateral meniscal extrusions, and joint space width. Specifically, the T2 values were first converted to ranks and these ranks were then used as the dependent variable for the ANCOVA. The ANCOVA model included alignment (varus versus valgus) as a classification factor and the subject-level factors adjusted for as covariates. Due to the relatively large number of potentially correlatable covariates, only significant independent covariates were retained in the final model for each T2 measure. The same method was used to compare the joint alignment groups in terms of KL scores adjusted for covariates. Exact Mann-Whitney tests were used to compare the joint alignment groups in terms of the measures of medial and lateral meniscal extrusion and joint space width. Fisher's exact test was used to assess whether the joint alignment groups differed in terms of the prevalence of medial or lateral meniscal extrusion. Spear-man rank correlation coefficients were used to test the correlation of T2 values with patients' age, KL scoring, measures of medial and lateral meniscal extrusion, and joint space width. All reported *P* values are two-sided, were not subjected to a multiple comparison correction and were declared statistically significant when *P* < 0.05.

Results

The median $\pm$ IQ range of the KL scores was 2.0 $\pm$ 1.75 among patients with valgus alignment and 3.5 $\pm$ 1.0 among patients with varus alignment. After adjustment for covariates, KL scores were significantly higher (*P*=0.0467) among patients with varus alignment than patients with valgus alignment. No statistically significant association between the T2 values of cartilage in any of the locations (MFC, MTP, LFC, LTP) and the KL score was found in the varus group or in the valgus group.

Meniscal tears were found in 18 of the 24 patients included in this study, ACL tears were found in 2 patients.

The overall T2 value of cartilage (median $\pm$ inter-quartile range) was 48.16 ± 7.05 ms. The T2 values of cartilage of the medial compartment (MFC and MTP; 49.44 ± 6.58 ms) were significantly higher than those of the lateral compartment (LFC and LTP; 47.15 ± 6.87 ms; $P=0.0043$); the values of the tibial plateaus (MTP and LTP; 47.35 ± 6.67 ms) were lower than those of the femoral condyles (MFC and LFC; 48.85 ± 6.88 ms; $P=0.1156$), with no statistical significance.

The T2 values of cartilage in patients with valgus as well as with varus alignment for the MFC, the LFC, the MTP and the LTP are listed in Table 1. Overall, after adjusting for covariates, the T2 values of cartilage in patients with varus alignment were higher ($P<0.0001$) than those in patients with valgus alignment.

More localised, after adjusting for covariates, a significant varus versus valgus difference was found for the T2 values of the MFC ($P=0.001$), the MTP ($P=0.0001$), the LFC ($P=0.0081$), and the LTP ($P=0.0329$). Comparing compartments, statistically significant differences between patients with varus and valgus alignment were noted for all compartments: medial compartment (= MFC + MTP; $P<0.0001$), lateral compartment (= LFC + LTP, $P=0.0015$), femoral condyles (= MFC + LFC, $P=0.0002$), and tibial plateaus (= MTP + LTP, $P=0.0008$).

The mean BMI of the patients was 27.4 ± 2.7 . The BMI was within the normal range in 2 patients (8%); 15 patients were overweight (63%), 6 obese (25%), and BMI was unknown in 1 patient (4%).

Three of the 12 patients with varus alignment were overweight (25%); 9 patients were obese (75%). No statistical differences between the overweight and obese groups were found in terms of T2 values of cartilage in patients with either varus (medial compartment, $P=0.1400$; lateral compartment, $P=0.7662$) or with valgus alignment (medial compartment, $P=0.3834$; lateral compartment, $P=0.5814$).

All but five patients had either medial ($n=5$) or lateral ($n=4$) or medial and lateral ($n=10$) meniscal extrusion. There was a statistically significant correlation between KL scores and extrusions of the medial meniscus ($P=0.0058$), but not of the lateral meniscus ($P=0.8221$). Extrusions of the lateral meniscus were seen to be more frequent among subjects with varus alignment (75%, 9/12) than among subjects with valgus alignment (41.7%, 5/12). Similarly, extrusions of the medial meniscus were seen to be more frequent among subjects with varus alignment (66.7%, 8/12) than those with valgus alignment (58.3%, 7/12). However, there was no significant difference between varus and valgus patients in terms of the frequency of either lateral ($P=0.2138$) or medial meniscal extrusion ($P=1.0$).

The joint space width in the medial compartment was smaller in patients with varus alignment (median $\pm$ inter-quartile range, 0.09 ± 0.27 cm) than in patients with valgus alignment (0.48 ± 0.29 cm; $P<0.001$), but in the lateral compartment, no such difference was found (varus 0.68 ± 0.30 cm; valgus 0.68 ± 0.17 cm; $P=0.9889$). Moreover significant correlations between the T2 values of cartilage in the MFC ($P=0.0178$) and the MTP ($P=0.0203$) and the medial joint space width were observed. There was neither significant correlation between the T2 values of cartilage in the LFC ($P=0.8760$) and the LTP ($P=0.6229$) and the medial joint space width nor between the T2 values of cartilage in the MFC ($P=0.5285$), MTP ($P=0.8048$), LFC ($P=0.5849$), or LTP ($P=0.3913$) and the lateral joint space width.

No significant correlation between the T2 values of cartilage and patients' age was found, neither in patients with varus (MFC, $P=0.1858$; MTP, $P=0.5486$; LFC, $P=0.4907$; LTP,

$P=0.3654$) nor in those with valgus alignment (MFC, $P=0.8287$; MTP, $P=0.5862$; LFC, $P=0.6092$; LTP, $P=0.5049$).

Discussion

Biomechanically, cartilage loss and resultant joint space narrowing in the medial compartment can typically lead to varus malalignment. Varus positioning causes the axial loading vector to pass more medially during ambulation. This results in increased loads across the medial compartment, as indicated by the external knee adduction moment measured during gait analysis [2]. It has also been shown that a 1-unit increase in the knee adduction moment results in a 6.46-fold increase in the risk of medial disease progression [17].

Malalignment has been identified as an important risk factor for structural progression of femorotibial OA as observed on weight-bearing radiographs [18, 19]. In knees with varus alignment, analyses showed significantly increased progression [18]. These observations are supported by the results of this study, which report significantly higher KL scores among patients with varus alignment than patients with valgus alignment. However, these previous radiographic assessments have limitations. Measurements of joint space narrowing in the less-loaded compartment may not be meaningful because of pseudo-widening [20], and joint space narrowing measurement may reflect a change not only in cartilage but also in the meniscus [21].

This study documented a correlation between knee joint alignment and a biochemical imaging marker for cartilage degeneration: T2 values of cartilage were significantly higher with varus than with valgus alignment in this medial OA patient study population.

Sharma et al. reported that varus alignment increased the risk of cartilage loss in medial cartilage surfaces, as seen on morphological MR imaging [22]. Another study demonstrated that the correlation of the hip-knee-ankle angle with medial versus lateral cartilage loss was somewhat stronger for cartilage thickness than for cartilage volume, because there was some increase in the subchondral bone area between baseline and follow-up. In the medial femorotibial compartment, the correlation was significant for the tibial, but not for the femoral cartilage, whereas in the lateral femorotibial compartment it was significant for the femoral but not for the tibial cartilage [23]. Although this study is not directly comparable with our study, as for example we did not use the hip-knee-ankle angle for the assessment of alignment, it is still remarkable that, in our study, in the MFC, MTP, LFC, and LTP statistically significant differences were found between the T2 values of cartilage in patients with varus alignment. Moreover our study did not find any statistically significant association between the T2 values of cartilage in any location (MFC, MTP, LFC, LTP) and the KL scores in the varus and in the valgus group. This observation is consistent with prior reports. For example, Dunn et al. found that the differences between the least squares mean T2 values of patients with mild OA (KL scores 1 and 2) and those with severe OA (KL scores 3 and 4) were not significant for any cartilage compartment [6]. The lack of significant association between T2 values and KL scores might also indicate the advantage of using T2 mapping as a biochemical, more sensitive and better quantifiable, imaging marker over other strictly morphological imaging criteria as a means of assessing cartilage changes in OA. T2 mapping might also be able to show an association between knee malalignment and incident knee osteoarthritis, which—contrary to the evidence that knee malalignment is an independent risk factor for progression of knee OA—morphological imaging has never been able to prove. If we are to treat these patients with anything other than salvage procedures, improved understanding of pre-structural disease is required.

One could also argue that meniscal extrusion was a major contributor affecting knee joint alignment thus influencing the T2 values of cartilage. However, in this study we found no significant difference between varus and valgus patients in terms of the frequency of either lateral or medial meniscal extrusion.

This study also showed that measurements of joint space width alone were not sufficient to predict T2 values of cartilage, because although there *was* a significant correlation between the T2 values of cartilage in the MFC and the MTP and the medial joint space width, there was *neither* a significant correlation between the T2 values of cartilage in the LFC and the LTP and the medial joint space width *nor* between the T2 values of cartilage in the MFC, MTP, LFC, or LTP and the lateral joint space width.

Rauscher et al. reported significantly lower T2 values of cartilage in patients (mean 30.31 ms) with mild OA (KL scores 1 and 2) as well as in healthy controls (mean 29.01 ms) than we found. However, they used a spoiled gradient-echo sequence with a nonselective T2 preparation pulse, while we used a MESE sequence. A prior study has shown that T2 values of cartilage assessed by such spoiled gradient-echo sequences are lower than those assessed by a MESE sequence [24]. Additionally, the choice of specific sequence parameters influences the T2 values [24].

Welsch et al. reported that the global mean T2 values of cartilage in healthy controls were 56.3 ± 15.2 ms within the femoral condyles and 43.6 ± 8.5 ms within the tibial plateaus [25]. Their values were higher than ours as expected because their study was performed at 7T, with consequent shorter T2 relaxation times.

One limitation of the present study is that we did not obtain full-limb radiographs for accurate measurement of mechanical alignment. Kraus et al. reported a mean offset of 4° in the valgus direction for anatomical alignment compared with mechanical alignment [26]. Full-length lower-extremity radiographs expose the patient to higher amounts of radiation, require greater technical expertise on the part of the radiology technician, and are more expensive than short knee radiographs. For these reasons, it is common for physicians treating early knee osteoarthritis to base their assessment, prognosis and treatment plans on radiographs that include only the knee [27]. Another limitation of the study is the relatively small study population. However, the major results of our study are highly significant. We did not find a statistically significant association among BMI, alignment and T2 values of cartilage, perhaps related to having only three obese patients in both the varus and in the valgus alignment groups.

We have demonstrated that knee joint alignment influences the T2 values of femorotibial cartilage in patients with clinical symptoms of medial OA. This might possibly indicate its role in disease development or progression. We believe that understanding the role that knee alignment plays in OA progression is important, because it modulates the effect of standard risk factors for knee OA progression including obesity, quadriceps strength, laxity and stage of disease.

In terms of treatment, surgical interventions are reserved for end-stage OA patients, although there is no controversy that more limited treatments are desirable. Besides drug therapies laterally wedged shoe insoles are one non-pharmacological treatment strategy for managing knee OA [28]. Kuroyanagi et al. showed that lateral wedged insoles significantly reduce the knee varus moment during walking compared with the barefoot condition without insole [29]. T2 mapping could be used for quantitative assessment of outcomes in both surgical and conservative treatments improving joint alignment in early knee OA patients in the future.

In conclusion, this study demonstrated that T2 measurements were increased in medial knee OA patients with varus alignment, adding support to the theory of an association of OA and joint alignment.

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Fig. 1.

A 54-year-old female patient with clinical symptoms of medial OA and a KL score of 3. **a** AP, weight-bearing radiograph of both knees with alignment measurement lines. The measured angle is 183° for the left knee indicating valgus alignment. Sagittal T2 maps of cartilage for the medial (**b**) and lateral (**c**) compartments of the left knee. The mean T2 value of the medial compartment (44.92 ms) was not significantly different from that of the lateral compartment (43.44 ms) in this patient

Fig. 2.

A 59-year-old male patient with clinical symptoms of medial OA and a KL score of 3. **a** AP, weight-bearing radiograph of both knees with alignment measurement lines. The measured angle is 178° for the left knee indicating varus alignment. Sagittal T2 maps of cartilage for the medial (**b**) and lateral (**c**) compartment of the left knee. The mean T2 value of the medial compartment (56.10 ms) was significantly higher than that of the lateral compartment (49.63 ms) in this patient

Table 1T2 values (ms) of cartilage (median $\pm$ inter-quartile range) in varus and valgus alignment

Region	MFC	LFC	MTP	LTP
Varus alignment	53.77 $\pm$ 3.99	49.97 $\pm$ 3.93	52.72 $\pm$ 3.59	47.83 $\pm$ 4.16
Valgus alignment	47.23 $\pm$ 3.70	45.28 $\pm$ 10.58	46.54 $\pm$ 3.85	42.60 $\pm$ 8.49