Knee Surg Sports Traumatol Arthrosc (2014) 22:1396–1403
DOI 10.1007/s00167-013-2756-9

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Alignment does not influence cartilage T2 in asymptomatic knee joints

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Received: 12 January 2013 / Accepted: 28 October 2013 / Published online: 29 November 2013

Abstract
Purpose To investigate whether the static knee alignment affects articular cartilage ultrastructures when measured using T2 relaxation among asymptomatic subjects.
Methods Both knee joints ($n = 96$) of 48 asymptomatic volunteers (26 females, 22 males; 25.4 ± 1.7 years; no history of major knee trauma or surgery) were evaluated clinically (Lysholm, Tegner) and by MRI (hip–knee–ankle angle, standard knee protocol, T2 mapping). Group ($n = 4$) division was as follows: neutral (<1° varus/valgus), mild varus (2°–4° varus), severe varus (>4° varus) and valgus (2°–4° valgus) deformity with $n = 12$ subjects/group; $n = 24$ knees/group. Regions of interest (ROI) for T2 assessment were placed within full-thickness cartilage across the whole joint surface and were divided respecting compartmental as well as functional joint anatomy.
Results Leg alignment was 0.7° ± 0.5° varus among neutral, 3.0° ± 0.6° varus among mild varus, 5.0° ± 1.1° varus among severe varus and 2.5° ± 0.7° valgus among valgus group subjects and thus significantly different. No differences between the groups emerged from clinical measures. No morphological pathology was detected in any knee joint. Global T2 values (42.3 ± 2.3; 37.7–47.9 ms) of ROIs placed within every knee joint per subject were not different between alignment groups or between genders, respectively.
Conclusion Static frontal plane leg malalignment does not affect cartilage ultrastructure among young, asymptomatic individuals as measured by T2 quantitative imaging.
Level of evidence Cross-sectional study, Level II-III.

Keywords Malalignment · Cartilage · T2 Mapping · MRI

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Introduction

Osteoarthritis (OA) is an increasingly common disease, in particular at the knee joint [12]. As the success of OA treatment is still limited, preventive strategies are wanted [14, 27, 39]. A paucity of risk factors for OA has been identified already [51], while several causative pathomechanisms are still under extensive investigation. Alteration to frontal plane static knee alignment is regarded as one compound to be associated with developing OA at the lower limb [41]. A recent systematic review provided the information that malalignment of the knee joint represents an independent risk factor for the progression of OA, while

there remains controversy concerning malalignment and the risk of incident OA [45]. Janakiramanan et al. [26] reported that pathological changes to the mechanical axis are associated with the risk of compartment-specific knee cartilage defects in both healthy and arthritic people. Chondral defects may progress [4, 5] and are known to predate further cartilage loss and possibly associated meniscus lesions. However, it still remains unclear whether asymptomatic malalignment results in cartilage impairment or alters the physiological performance of the knee joint. This knowledge may influence future treatment algorithms for young patients that are occupied by genu varum/valgum deformities when early prevention is considered. Conventional radiographs may identify signs of progressive OA manifestation such as joint space narrowing or osteophyte formation. On the other hand, standard radiographs deliver several limitations as degenerating structures are not directly imaged; for example, joint space narrowing can result from both cartilage and meniscal degeneration and shows a high variability among subjects [25]. Obliged to recent advances in non-radiant musculoskeletal imaging, quantitative magnetic resonance imaging (MRI) sequences such as delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC), T1ρ or T2 mapping [31, 37] allow for non-invasive exploration of articular cartilage and a potential prevailing pathology, which may progress silently with increasing age [30]. In particular, T2 value impairment is regarded as a pre-structural indicator of OA since it is correlated with pathological changes at the cartilage water content and/or collagen architecture, which are changes not to be identified by conventional radiography or even current standard MRI [7]. The aim of the study presented here was to analyse knee joint cartilage ultrastructure among otherwise healthy subjects that are occupied by a native lower limb axis disturbance utilizing quantitative T2 mapping techniques. Considering the controversy regarding malalignment and incidence of OA, we hypothesize that frontal plane knee malalignment among asymptomatic individuals does not affect cartilage ultrastructure as analysed via quantitative MR imaging.

Materials and methods

A total of 96 knee joints of 48 non-smoking, healthy volunteers (26 females, 22 males, 22–30-year old, BMI 18–25) without any history of significant trauma, rheumatic disease, surgical intervention or ligament instability in either knee joint or any other joint-related pathology were recruited from the authors' circle of friends. They were examined by one orthopaedic surgeon and subdivided into four groups using the static mechanical axes (line of Mikulicz) of both lower extremities. Group division ($n = 12$ subjects per group; $n = 24$ knees per group) according to alignment was as follows: neutral group 0 (<1° varus/valgus deformity), mild varus group 1 (2°–4° varus deformity), severe varus group 2 (>4° varus deformity) and valgus group 3 (2°–4° valgus deformity). Clinical evaluation, including BMI calculation, was captured using the modified Lysholm score and Tegner activity rating scale [46]. Standardized weight-bearing, frontal plane, full-length, digital photographs of both legs in bipedal stance for the measurement of static knee joint alignment were captured in the first place as previously described [40]. Values obtained via digital photography were then reappraised via MRI techniques as described below.

Imaging procedures

Both knee joints of every participant were assessed by standard MRI at 1.5 T in supine position (Siemens Avanto; Siemens Medical Solutions, Erlangen, Germany), equipped with 40 mT/m gradients, utilizing a dedicated 8-channel knee coil (Medical Advances, Milwaukee, WI, USA). An adapted knee protocol [38] was acquired in all participants consisting of a sagittal T1-weighted turbo spin-echo (tse) sequence with a driven equilibrium (DRIVE) pulse, a field of view (FOV) of 16 cm, section thickness of 3 mm, a acquisition matrix of 384 × 384 and a bandwidth of 64 Hz/pixel. The T1-w sequence had a TE of 15, a TR of 647 and an ETL of 3. In average, 26 sections were obtained in 4:30 min. Furthermore, a 3D T2-w fat set (fs) driven equilibrium in the steady-state (DESS) sequence with a voxel size of 0.5 × 0.5 × 0.7 mm (TE 6.9, TR 18.9) and a 3D T1-w gradient echo sequence with a voxel size of 0.25 × 0.25 × 1.2 mm (TE 5.7, TR 11.7) were obtained each in 6 min. T2 relaxation time acquisition was accomplished by T2 mapping in the sagittal plane of all articulating joint surfaces. A multi-echo spin-echo acquisition was acquired with a TR of 1,690 ms and 6 TEs (10, 20, 30, 40, 50 and 60 ms), a FOV of 17 × 13 cm, an acquisition matrix of 384 × 288 at a bandwidth of 64 Hz/pixel resulting in a time of acquisition of 6:04 min and an interpolated pixel size of 0.22 mm. In addition, static frontal plane knee joint alignment of both lower extremities was determined using a previously established MRI-based measurement technique [22]. In brief, coronal T1-weighted images centred to the ankle, knee and hip joint were acquired, and full-leg images were obtained by image composition. On the basis of these encoded images, MR-based hip–knee–ankle alignment of both lower extremities was measured and additionally compared to values obtained via digital photography. Groups were then divided according to the MR-based data.

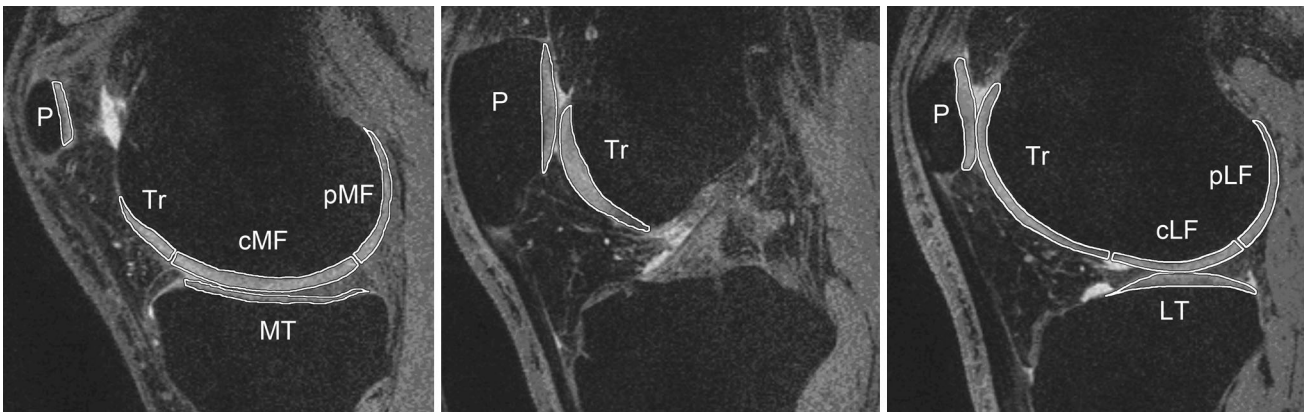

Fig. 1 Division and nomenclature of the femoral, tibial and patellar cartilage segments respecting compartmental and functional knee joint anatomy with modifications according to the proposed nomenclature by Eckstein [8]. Regions of interest: cMF, pMF and MT at the medial tibiofemoral compartment; P and Tr at the patello-femoral compartment; cLF, pLF and LT at the lateral tibiofemoral compartment

Evaluation of images

T2 relaxation time maps were calculated pixel-wise in the multi-echo spin-echo images (echoes 2–6, with exclusion of the first echo to avoid artefacts by stimulated echoes) using a monoexponential non-negative least-squares fit analysis with a custom-built software (IDL, Creaso, Gilching, Germany) [6]. Regions of interest (ROI), with modifications, were suited to the realms of full-thickness cartilage and subdivided in a view of different levels of strain roughly based on the consensus recommendation for anatomically adapted labelling as described by Eckstein et al. [8]. For that, the margins between trochlea, central and posterior femoral compartments were defined by a cutting line orthogonal to the cartilage surface and adjacent to the anterior and posterior horn of both menisci, respectively (Fig. 1). Femoral (F) ROIs were stated as medial (MF) and lateral (LF) and subdivided into central (cMF, cLF) and posterior (pMF, pLF). Equally, tibial ROIs were set as medial tibia (MT) and lateral tibia (LT) and not further subdivided. The articulating surface of the patella (P) and the trochlea (Tr) was not further subdivided regarding the potentially shifting levels of strain at the patello-femoral joint in malaligned knees [10]. In order to minimize intersubject variability in positioning, manual ROI adjustment was performed simultaneously by two investigators in consensus (one orthopaedic surgeon and one radiologist). In previous studies, this technique showed an acceptable reproducibility error between 1.7 and 5.7 % in case of healthy cartilage [38].

To investigate other sources of patello-femoral joint malalignment or dysplasia, the tibial tuberosity–trochlear groove (TTTG) distance and the trochlear sulcus angle were measured in axial reformations of the DESS sequence.

Institutional review board approval

The study was performed in accordance with the Declaration of Helsinki. Informed consent from each participant was obtained prior to investigation. Institutional review board approval was given by the local ethics committee (Technical University Munich; project ID 2227/08).

Statistical analysis

A sample size of 22 knees per group delivers 80 % power to detect a T2 difference in the means of 3.1 ms (the difference between T2 relaxation time in healthy cartilage, mean 34.2 ms, and in cartilage affected by mild OA, mean 37.3 ms [7]), assuming the standard deviation with ± 3.5 ms using a two-group Satterthwaite *t* test with a 0.05 two-sided significance level. Respecting the stated sample size calculation and concerning our resources of volunteers, we finally included a total of 24 knees per group.

The major determinant for outcome comparison was the mechanical axis division according to the alignment groups described above. Statistical analysis was performed using the software package SPSS version 17 (SPSS Inc, Chicago, Illinois, USA). All data were tested for normal distribution using the Kolmogorov–Smirnov test. Group data were compared using univariate ANOVA corrected for cofounding variables (age, gender, BMI). To control the family-wise error rate, the Bonferroni correction was applied. Unless otherwise stated, descriptive results were demonstrated as the mean ± standard deviation (SD). Significance was set at $P < 0.05$ for all tests.

Table 1 Gender (male/female), age at time of examination, body weight in kg, height in cm, BMI, Tegner activity scale, both knee-combined Lysholm score, both knee-combined values in degree for mechanical axis in subjects with neutral, mild varus, severe varus and valgus alignment of both lower extremities ($n = 12$ subjects, $n = 24$ knees/group), mean ± SD

	Gender	Age	Weight	Height	BMI	Tegner	Lysholm	Axis
Neutral	4/8	25.3 ± 1.7	64.9 ± 8.3	176 ± 8	21.0 ± 1.3	6.4 ± 1.8	97.0 ± 4.5	0.7 ± 0.5
Mild varus	10/2	25.7 ± 1.2	72.1 ± 8.6	179 ± 9	22.5 ± 1.5	7.8 ± 1.7	96.6 ± 4.9	3.0 ± 0.6
Severe varus	7/5	26.0 ± 2.3	72.0 ± 9.2	181 ± 6	21.7 ± 1.9	7.5 ± 1.8	97.3 ± 4.7	5.0 ± 1.1
Valgus	1/11	24.5 ± 1.3	61.5 ± 6.5	170 ± 5	21.4 ± 2.0	6.2 ± 1.4	96.5 ± 5.7	−2.5 ± 0.7

Significance provided within "Results" section

Results

Participant characteristics

An overview of participant characteristics is given in Table 1. All patients were without knee complaints, and clinical knee examination was without pathological findings. There was a significant overall group difference for weight, height, BMI ($P < 0.05$) as well as for axis deviation measured via digital photography ($P < 0.001$) and via MRI ($P < 0.001$), respectively. Lysholm and Tegner scores for isolated (left, right) as well as for both knee joints/subject each were not different between groups. All malalignment values obtained via digital photography and MRI (as well as the combined value per knee/subject) were significantly different for every possible group comparison, respectively. Neither alignment values measured via digital photography nor MR-based alignment values (right vs. left) were significantly different per knee/subject. There was no difference when comparing the alignment values obtained via digital imaging with MR-based values.

MR outcome

There was no intra-articular, no ligamentous and particularly no meniscal or cartilage pathology in any knee joint, analysed in the standard morphological MRI protocol. The soft tissue surrounding the knee joint was as well without pathological findings. An overview of the quantitative MR outcome is given in Table 2, Figs. 2 and 3. Global T2 values (42.3 ± 2.3; 37.7–47.9 ms) of ROIs placed within every knee joint per subject were neither different between alignment groups nor between genders, respectively. Comparing T2 values of the single anatomical regions, there was also no significant difference between all alignment groups. None of the investigated possible confounding factors gender, age and BMI showed a significant influence ($P < 0.05$). As differences between the groups also were independent of these factors, only original values are given in the following. Highest global T2 value was found in Tr with 47.1 ± 3.1 ms, while P produced the lowest global T2 with 38.7 ± 3.5 ms. Regional T2 difference between right- and left-sided knee joints never reached the level of significance. There were trends towards higher T2 values in MT than in LT and in cLF than in cMF among varus-aligned groups, while the reverse holds true among valgus-aligned subjects. Those findings never reached the level of significance.

Both TTTG distance and trochlear sulcus angle were within normal range in all subjects (TTTG average 7 mm, all <1.8 cm, sulcus angle average 123°, all <134°).

Discussion

Isolated mechanical axis malalignment was not associated with cartilage ultrastructure deterioration in this study of a cohort of asymptomatic individuals investigated via T2 relaxation time mapping. In light of knee OA as a rising socio-economic burden, it is of paramount importance to examine any potential predisposition for disease incidence or progression, in particular, if early intervention might be possible [13]. Frontal plane knee mechanical axis malalignment is considered as an independent risk factor for the progression of OA [45], while strong controversy persists regarding malalignment and incidence of OA. In our study, no association between knee malalignment and cartilage integrity, as well as physical activity, was found in 96 knees of healthy, young volunteers.

This is in accordance with the previous studies, showing that altered loading without pre-existing structural damage is not a risk factor for knee OA [23, 24, 34]. In elderly subjects with and without osteoarthritis, controversial findings were reported: alterations of the mechanical axis were associated with compartment-specific cartilage defects in patients older than 40 years [26]. However, the association with other injuries like meniscal defects was not investigated; thus, the pathophysiological onset remains unclear. In elderly subjects, many risk factors for OA have been identified, in particular obesity and structural damages to ligaments and menisci [12, 24, 45, 48]. In this study, we examined healthy, young, normal-weighted

Table 2 Global and knee joint region divided (M = medial, L = lateral, c = central, p = posterior, F = femur, T = tibia, Tr = trochlea, P = patella) T2 relaxation in ms among subjects with neutral, mild varus, severe varus and valgus alignment of both lower extremities (n = 12 subjects, n = 24 knees/group), mean ± SD

	cMF	cLF	pMF	pLF	MT	LT	Tr	P
Neutral	42.0 ± 3.3	41.3 ± 2.9	41.5 ± 4.0	43.2 ± 2.8	40.8 ± 4.0	40.0 ± 3.7	45.8 ± 3.1	37.7 ± 3.1
Mild varus	43.2 ± 3.4	43.6 ± 4.5	42.4 ± 4.1	43.9 ± 4.1	42.8 ± 2.7	41.5 ± 3.2	47.9 ± 3.2	39.7 ± 4.3
Severe varus	42.3 ± 2.3	42.9 ± 2.6	42.3 ± 2.1	44.6 ± 3.6	42.4 ± 3.0	41.0 ± 3.4	47.8 ± 2.2	38.8 ± 3.0
Valgus	41.8 ± 3.1	41.0 ± 3.5	41.3 ± 3.4	42.8 ± 4.1	40.6 ± 3.0	41.0 ± 2.7	46.8 ± 3.6	38.8 ± 3.5
Global T2	42.3 ± 3.1	42.2 ± 3.6	41.9 ± 3.5	43.6 ± 3.7	41.7 ± 3.3	40.9 ± 3.3	47.1 ± 3.1	38.7 ± 3.5

Significance provided within "Results" section

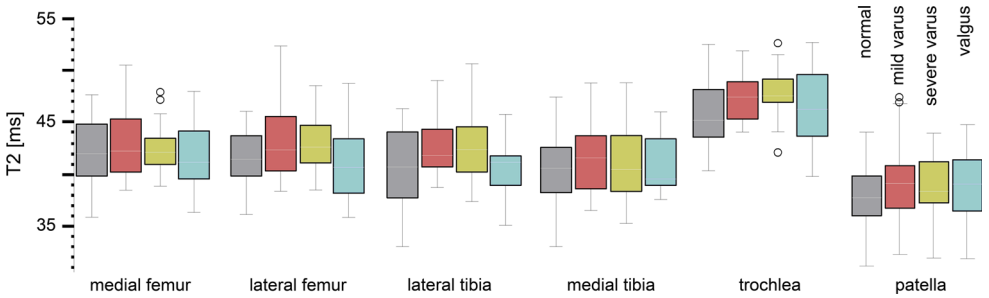

Fig. 2 T2 values in ms of selected knee joint regions: weight-bearing medial (cMF), lateral femur (cLF), weight-bearing lateral (LT) and medial (MT) tibia as well as the patello-femoral joint (Tr, P) among subjects with neutral, mild varus, severe varus and valgus mechanical axis alignment of the lower extremities (n = 12 subjects, n = 24 knees/group). Median and inter-quartile range. Significance provided within the "Results" section

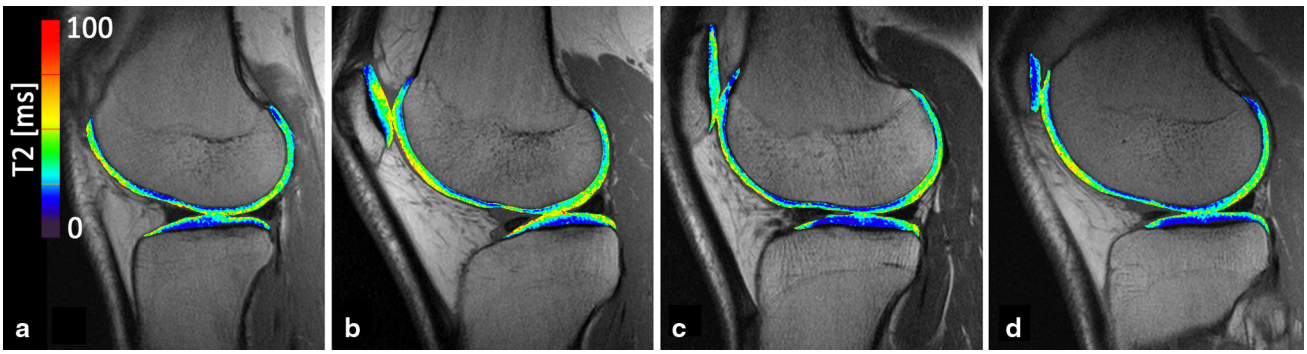

Fig. 3 Colour-coded T2 maps of the lateral knee joint (LT, LF) of four asymptomatic volunteers with different mechanical axis alignment of the lower extremities: *A* valgus; *B* neutral; *C* varus; *D* severe varus, corresponding to the four groups compared

adults to exclude all these known risk factors and investigate the sole effect of malalignment on (ultra-) structural cartilage deterioration. Varus alignment is a common observation that has been described to be more frequent in specific populations participating in sports such as soccer [49]; of note, varus malalignment of the lower extremities does not limit the physiological performance of the affected subjects [30]. Such information is much more rare in valgus knee joints, which as well have been identified to increase the incidence of OA [13]. Multiple compounds have been described to have detrimental effects on the medial joint compartment [41], which carries higher loads and has been described to be particularly susceptible to irregularities within the mechanical axis due to increased adduction moments, medial ligament laxity or superior vastus medialis muscle function [30, 47]. The same holds true for the lateral knee compartment, which, however, has been investigated with lesser frequency [13], while also progression of patello-femoral OA is claimed to be associated with frontal plane knee malalignment [10, 21]. Preventive intervention to neutralize the mechanical load within the knee joint among asymptomatic individuals is an unexpressed matter of debate, while currently a decision would not be supported by the scientific evidence. Yet,

paradigms to address malalignment are available; however, there is indeed no ratio to treat asymptomatic patients: knee and foot orthoses as initial conservative treatment modalities have shown improvement in function and pain among subjects with severe clinical symptoms [3, 35], while corrective osteotomies across the knee joint may result in improved function and pain among patients suffering from unicompartmental OA [2, 36].

However, all such corrective interventions or conservative attempts impose their positive effect only on symptomatic knee joints that are burdened with cartilage impairment or OA already while we still lack information concerning a doubtable negative influence of malalignment on healthy, asymptomatic knees. It is still not clear whether malalignment results in articular cartilage impairment, vice versa or bidirectional. Based on the findings of the study presented here, we conclude that existing, atraumatic varus/valgus malalignment does not show any signs or symptoms of disease and does not produce cartilage ultrastructural alteration in the assumed mechanically overloaded compartments as measured via quantitative MRI. T2 relaxation time measurements have been used, as T2 has been reported to be sensitive particularly to early changes in cartilage degeneration [1, 28].

Previous studies have reported that pre-structural cartilage alteration is greater at the tibial plateau than in the femoral compartments [47], which may be related to higher chondral susceptibility. When comparing neutral with mild and severe varus knee groups, we only found the slight tendency of T2 relaxation differences, with generally higher values in varus-aligned knees, regularly at the medial tibia (MT) while valgus-aligned subjects produce higher T2 at the lateral tibia. These elevated T2 values may represent adaption to biomechanical load in the form of previously reported increased water content [32] and/or collagen assimilation [15] while the correct interpretation of elevated as well as depressed T2 values has yet to be elucidated. Running itself has been reported to result in decreased T2 values. This occurs most likely due to reversible, physiologically depleted water content within superficial cartilage. Mosher reported on the elevation of cartilage T2 in asymptomatic subjects over 45 [34], while the same group reported longer T2 among young marathoners versus young control subjects (difference not significant), potentially in light of chronic mechanical stimulation. This trend was not evident in older subjects, while it is known that articular cartilage among this cohort is much stiffer.

Significantly increased T2 values, compared to healthy controls, under excessive load have been also described in active early OA subjects with focal cartilage abnormalities [43]. Remarkably, there was no significant difference in T2 relaxation in our cohort of participants even when comparing knees with neutral alignment to those occupied with 5° of varus malalignment. This may indicate malalignment to facilitate cartilage impairment if already established, while healthy cartilage demonstrates the capacity to compensate for variant biomechanical loading.

The patello-femoral joint has been described to be affected by alignment alterations as well [10]. In this study, patello-femoral dysplasia was excluded by measurements of TTTG distance and sulcus angle. However, T2 times still might be influenced by several other factors in this specific compartment. Flow artefacts were present in some images and may constitute a problem for the calculation of a reliable T2 time. However, it should be similar for all groups and also for the patella, where substantially lower T2 values were found as compared to the trochlea. The main reason for these differences may be the magic angle effect, as the main part of the trochlea is aligned in about 55° to the main magnetic field [18, 50]. In controversy to these inter-site differences, patellar as well as trochlear T2 values were similar among all alignment groups. These findings are underlined by the fact that the patellar undersurface is covered by a rather thick hyaline matrix related to overall highest biomechanical forces during locomotion, which has been described to result in different extracellular matrix [9], deformation, compensation capabilities [17] as well as chondrocyte function [19]. Patello-femoral compounds offer the capability of compensation of mechanical overloading in particular in young subjects. However, other studies have reported that patellar undersurface T2 values are affected by activity, OA or BMI [44]. Paralleling the interpretation of elevated/depressed T2 times, there is generally no consensus about normal T2 times, which are reported significantly different between studies [33], which is usually related to varying acquisition and/or post-processing techniques. Control subjects have to be included into every study to be able to draw intra-study comparisons, while isolated literary information is sparse as well [20, 42]. Hannila et al. [20] were the first who reported a topographical variation of T2 times among young, healthy subjects. Friedrich et al. [16] have previously reported on medially elevated T2 values in varus-aligned OA patients with a mean age of 62.5. In comparison, we found no significant differences in healthy, young subjects, indicating that the T2 elevation reported by Friedrich et al. may be due to compartment-specific changes in OA, not present in young and healthy volunteers.

The menisci within the knee joint play a major role in particular to protect and serve its surrounding cartilage [11, 24, 29]. Combining these and our results, it appears that as long as meniscal integrity is assured, malalignment and varying biomechanical strain may be well compensated by the succeeding collaboration of menisci and hyaline cartilage, and malalignment alone is not capable to impose

cartilage deterioration, while it may be a confounding factor for the worse if combined with some compartment-specific traumatic event. Yet, further quantitative investigation has to be conducted for the evaluation of potential meniscal alteration among malaligned subjects.

Some limitations have to be considered in the present study. The female/male ratio among participants was, concerning the groups, rather uneven. However, the named issue does not claim an impact on the study outcome since there was no gender difference to be detected, and furthermore, it rather presents a real-life situation since male subjects are more often affected by leg deformity when compared to female subjects. MRI was performed at 1.5T yielding a lower spatial resolution and/or signal-to-noise ratio as compared to 3.0T scanners. There remains a lack of analysis concerning T2 variation along the cartilage depth, such as superficial and deep zones of the cartilage; however, different loading affects the whole cartilage thickness and thus should result in T2 changes of the whole compartment. Gender differences were evident in particular when comparing the severe varus and valgus groups; however, results remained similar with and without considering these differences in the statistical model.

Conclusion

Considering a persisting controversy concerning varus/valgus malalignment, it was demonstrated that articular cartilage of young, active, clinically asymptomatic adults illustrated no sign of alignment-dependent alteration as measured by T2 relaxation time mapping. Such information may contribute to a better understanding of compensatory capacities of articular cartilage and may help to establish a well-balanced decision process concerning OA prevention. Longitudinal studies will have to underline the data presented here.

Conflict of interest No authors had any financial or personal relationships with other people or organizations that could inappropriately influence this work. The authors declare that they have no conflict of interest.

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