Osteoarthritis Imaging 1 (2021) 100004

Contents lists available at ScienceDirect

Osteoarthritis Imaging

journal homepage: www.elsevier.com/locate/ostima

Cartilage collagen structure upon knee joint distraction and high tibial osteotomy as measured with T2-mapping MRI - post-hoc analyses of two RCTs

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ARTICLE INFO

Keywords:
Knee joint distraction
High tibial osteotomy
Joint-preserving treatment
T2 mapping
Cartilage
Collagen

ABSTRACT

Objective: High tibial osteotomy (HTO) and knee joint distraction (KJD) are joint-preserving treatments for knee osteoarthritis (OA) that have shown good clinical results and cartilage thickness increase. In this exploratory study, cartilage T2 relaxation times, as a measure of collagen structure, are evaluated after both treatments, and compared to natural OA progression.

Design: Ten patients indicated for total knee arthroplasty (TKA) were treated with KJD (KJD_{TKA}). Thirty patients indicated for HTO were treated with KJD (KJD_{HTO}; n = 10) or HTO (n = 20). 3T T2-mapping MRI scans were performed before and one (KJD groups only) and two years after treatment, from which cartilage was segmented and the volume and T2 relaxation times were calculated. Patients were matched with untreated patients from the Osteoarthritis Initiative (OAI) to compare the change in T2 values over time.

Results: KJD_{HTO} (n = 8) and HTO (n = 17) patients both showed statistically significant increases in T2 values (worsening) but no volume changes. KJD_{TKA} patients (n = 8) only showed a tendency for (first-year) T2 value increase, and a significant volume increase in the most affected compartment (MAC). There were no significant differences between the three groups. All treated patients combined showed a significantly higher increase in T2 times than untreated patients from the OAI for both femur and tibia.

Conclusions: KJD and HTO cause an increase in cartilage T2 relaxation times, which could indicate loss or reorganization of collagen structure integrity. In TKA-indicated KJD patients, this goes paired with volume increase, indicating it may be the result of maturation of newly formed cartilage.

Introduction

Cartilage degeneration and substance loss are hallmark features of knee osteoarthritis (OA). Cartilage thinning is an important parameter in the diagnosis of knee OA, in staging its severity and as outcome measure for monitoring disease progression and treatment effect [1,2]. Traditionally, cartilage thickness changes have been evaluated indirectly from radiographic joint space narrowing. Nowadays, MRI is frequently used for semi-quantitative scoring of OA-related parameters, but also to quantitatively measure cartilage thickness [3,4]. Quantitative analyses typically rely on 3D spoiled gradient recalled imaging sequences with fat suppression, which have been validated for measuring cartilage thickness and volume, but do not provide much information about cartilage quality [5]. In order to measure quality, sequences that can visualize cartilage composition are required, such as delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) and T2-mapping [6,7]. dGEMRIC MRI allows to depict the distribution of glycosaminoglycans, whereas T2-mapping is sensitive to changes in water content and the collagen fiber network, reflecting collagen content and orientation [8,9]. Compared to healthy cartilage, OA cartilage shows higher T2 relaxation times, as a result of loss of collagen content and matrix anisotropy (structure) and subsequent increase in permeability and water content [8,10–12]. T2-mapping is

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https://doi.org/10.1016/j.ostima.2021.100004
Received 8 July 2021; Received in revised form 14 October 2021; Accepted 15 October 2021

frequently used in observational studies [5], but has also been applied to investigate cartilage quality after cartilage defect treatment, where quality of the repair tissue can be compared to that of the surrounding native cartilage [7,10,13]. Cartilage T2-mapping is, however, not typically applied to evaluate the effect of joint-preserving surgical treatments for severe OA in whole (tibiofemoral) cartilage plates.

Two such treatments are high tibial osteotomy (HTO) and knee joint distraction (KJD), both used in younger knee OA patients to postpone a knee arthroplasty (KA). In KJD, the tibia and femur are temporarily placed at a distance with an external fixation frame, unloading the tibiofemoral compartments. In HTO, the mechanical leg axis is corrected by wedging the bone, unloading the most affected compartment (MAC) permanently [14,15]. Both treatments have shown not only good and comparable clinical results, but also cartilage restoration activity, demonstrated by radiographs, MRI-based cartilage thickness, and second-look arthroscopy as well as biochemical marker analyses [16–23]. Cartilage quality was previously evaluated with dGEMRIC, which showed that values after KJD and HTO treatment were on average not different from pre-treatment [24]. T2-mapping, however, has not yet been assessed and compared. The objective of this exploratory study was to evaluate cartilage T2 relaxation times as a measure of collagen structure before and after treatment with KJD and with HTO, and compare results between the two treatments. To compare these results to natural progression that might be expected in comparable, untreated OA patients, retrospective data from the OsteoArthritis Initiative (OAI) was used.

Patients and methods

Patients

Patients were included from two randomized controlled trials (RCTs). In one RCT, patients below the age of 65 years with indication total knee arthroplasty (TKA) were randomized to KJD (n = 20) or TKA (n = 40) treatment. In a separate RCT, patients with medial compartmental knee OA who in regular care were considered for HTO for medial compartmental knee OA were randomized to KJD (n = 23) or HTO (n = 46) treatment. Inclusion and exclusion criteria for both trials were primarily based on the indication TKA or HTO have been described previously; they included age < 65 years old, Kellgren-Lawrence grade (KLG) >2 (judged by orthopedic surgeon), no history of inflammatory disease, no surgical treatment of the involved knee < 6 months ago, and no primary patellofemoral OA [17,25].

After inclusion in one of the two RCTs, patients randomized to treatment with KJD or HTO were asked to participate in an extended imaging protocol, extending the standard MRI scans performed in all patients with additional modalities, including T2-mapping. The first 20 HTO patients and the first 20 KJD patients (irrespective of the trial from which they originated) who gave written informed consent for the extended imaging protocol were included. From the KJD *vs* TKA trial, 10 KJD patients were included (KJD_{TKA}); from the KJD *vs* HTO trial 10 KJD patients (KJD_{HTO}) and 20 HTO patients were included. It was previously shown that patient demographics of these subgroups of KJD and HTO patients participating in the extended imaging protocol did not significantly differ from the original KJD and HTO groups, except for the proportion of male patients that was significantly higher in the whole HTO group, which was considered coincidental [24].

The original RCTs and the extended imaging protocol were granted ethical approval by the medical ethical review committee of the University Medical Center Utrecht (protocol numbers 10/359/E, 11/072 and 11/482/E). All patients gave written informed consent.

Treatment

The KJD treatment protocol has been extensively described previously [15,25]. In short, at surgery an external fixation device consisting of two dynamic monotubes was fixed medially and laterally of the knee joint, using bone pins. Over three days, the joint was gradually distracted to a total of 5 mm, confirmed radiographically, after which patients were discharged and allowed full weight-bearing, supported by crutches if needed. After six weeks of distraction, the frame was removed at day treatment, without further imposed rehabilitation protocol.

For HTO treatment, biplane medial-based opening-wedge osteotomy was performed, shifting the weight-bearing line laterally. The aim was to let the post-operative mechanical axis run laterally through the tibial plateau at 62% of its width (measured from the medial side), as described in more detail previously [16]. Patients were discharged after three days, followed by six weeks of limited weight-bearing. At 18 months, the plate was removed to allow imaging at two years.

Image acquisition

Multi-slice multi-echo spin-echo (MSME) T2-mapping scans were performed on a clinical 3T MRI scanner (Achieva 3T; Philips Medical Systems) using a 16-channel knee coil. T2 relaxation times were obtained from T2 maps reconstructed using sagittal SE acquisition, with eight echo times (TE) of 10, 20, 30, 40, 50, 60, 70, and 80 ms. The slice thickness was 3 mm, with a pixel matrix of 640×640 and a pixel size of 0.25×0.25 mm. In the same session, a sagittal proton-density weighted (PDW) scan with fat suppression was performed, with an echo time of 40 ms, slice thickness of 2.7 mm, pixel matrix of 528×528 mm and pixel size of 0.30×0.30 mm.

Scans were performed before treatment (baseline) and at one years and two years after treatment. HTO patients did not undergo MRI scans at one year due to the metal-plate *in situ*. Only patients with scans available for analysis at baseline and two-year follow-up were included in this study.

Image analysis

Segmentation was performed thrice for all images, by three independent observers (MJ, NB, CN; two PhD students and one postgraduate student, all with an education in clinical technology and general experience with imaging/segmentation). Based on initial experimental segmentation, a consensus was reached between the three observers on how to perform the segmentations. The knee joint was divided in four regions: lateral femur, medial femur, lateral tibia, and medial tibia. Segmentation began from the center of the joint and was performed on seven slices, counting outwards from the first slice without cruciate ligaments. As was done for the dGEMRIC analyses in this same group of patients, regions reached until the most anterior part of the tibia plateau; the posterior tibial region reached until the most posterior part of the tibia plateau; and the posterior femoral regions encompassed all visible cartilage [24]. Regions of interests (ROI) were drawn on the PDW images using in-house developed software (Experimental Analysis, Image Sciences Institute) and automatically applied on the T2-mapping images, where manual corrections could be performed if necessary.

From all scans, the volume (mm^3) and T2 relaxation times (ms) were calculated for each of the four segmented regions. Pixels with T2 relaxation times > 100 ms were excluded, as these were not realistic for cartilage, but instead likely represented the bone edge included in the ROI. An example image with the included ROI is shown in Fig. 1.

Untreated control group

The OAI used a comparable protocol with somewhat lower resolution for the acquisition of MSME MRIs [26]. Cartilage T2-times from the OAI were based on a quality-controlled manual segmentation of femorotibial cartilages and were used as an untreated group of OA patients. Cartilage T2 times were available at baseline, one year, and four years from previous analyses [27,28]. From the available subset of OAI

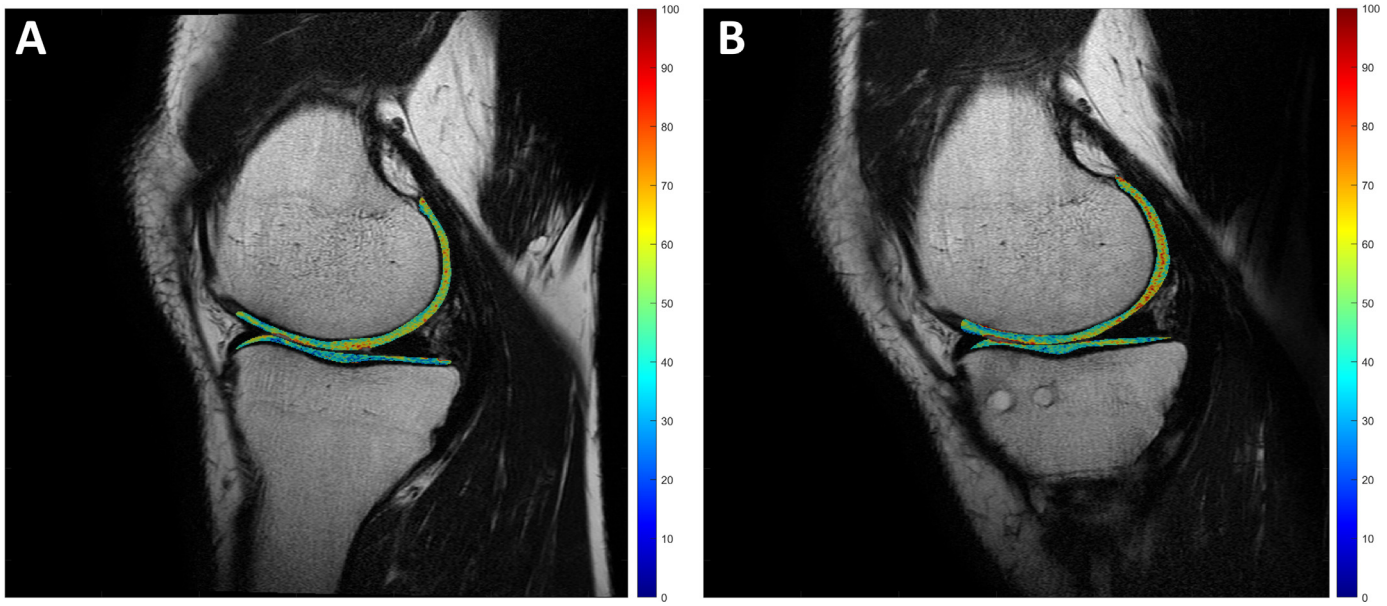

Fig. 1. Example of the reconstructed T2 map within the medial femoral and tibial region of interest, before (A) and two years after (B) treatment with high tibial osteotomy. Note the increased T2 values especially in the central weight-bearing region of the tibia and posterior region of the femur.

knees with T2-mapping results, control patients were selected with case-control matching, attempting to find a matched control patient for all treated (KJD and HTO) patients pre-treatment. Case-control matching was performed separately for the tibia (average of medial and lateral tibia) and femur (average of weight-bearing part of medial and lateral femur) and based on baseline T2 relaxation times as well as patient characteristics that had a significant influence on changes in T2 values in either group (treated or untreated). Tolerances were chosen as small as possible, while still ensuring the majority of treated patients could be matched with untreated OAI patients.

Statistical analysis

Baseline differences between the three groups (two KJD groups because of the different indication) were calculated with one-way ANOVA and, in case of statistically significant differences, post-hoc Tukey HSD tests.

The intraclass correlation coefficient (ICC) between the three observers was calculated for all T2 relaxation times and cartilage volumes, for each of the regions separately and combining all time points, using a two-way random model with absolute agreement. Assuming a good ICC for average measures, the results of the three observers were averaged to obtain the final T2 relaxation times and cartilage volumes. ICCs were interpreted according to the definitions of Koo and Li: an ICC < 0.50 was considered poor, 0.50 < ICC > 0.75 was moderate, 0.75 < ICC > 0.90 was good, and ICC > 0.90 was excellent [29].

Since previous research has shown that structural results are often significantly different between the most affected compartment (MAC) and least affected compartment (LAC) of the joint, which were determined at patient inclusion, results were separated in the MAC and LAC femur and tibia (instead of medial and lateral femur and tibia). For both KJD groups (for KJD_{TKA} and for KJD_{HTO}), the changes over time were calculated using repeated measures ANOVA. For differences in changes between these groups, mixed ANOVA was used, correcting for significantly different baseline characteristics. For the HTO group, the changes over time were calculated using paired t-tests, since only two time points were available. For differences in two-year changes between HTO and KJD_{HTO}, linear regression was used, correcting for baseline values and significantly different baseline characteristics.

Pearson correlations were calculated between one- and two-year changes in T2 values and volumes, for each compartment and group separately. As an additional exploratory analysis between changes in T2 values and clinical outcome, Pearson correlations were calculated between two-year changes in T2 values/volumes and visual analogue score of pain (VAS pain; filled out by patients at the same time points MRI scans were performed). This was done for each compartment and group separately as well.

Since different time points were available for KJD patients, HTO patients and OAI patients, regression coefficients were calculated for the average tibia and average femur T2 relaxation times for each patient separately, including all available time points, to represent changes over time (ms/year).

The influence of baseline characteristics on the change in tibia and femur T2 relaxation times for each of the three treated patient groups and the untreated OAI patients separately, using these regression coefficient in linear regression models. Each characteristic and baseline value was evaluated in separate models.

To compare treated patients with the matched OAI untreated patients, regression coefficients were compared using linear regression, correcting for statistically significant differences in baseline characteristics between the groups.

Continuous variables are given with mean and standard deviation, categorical variables with n and %; changes over time are given with mean change and 95% confidence interval (CI). For all tests, $p < 0.05$ was considered statistically significant.

Results

Patients

For the KJD patients, four patients did not have complete T2-mapping datasets because of either motion artefacts, refusal for follow-up or conversion to another treatment (HTO or TKA), resulting in 8 KJD_{TKA} and 8 KJD_{HTO} patients. For the HTO patients, three patients did not receive the extended imaging at two years: one was MRSA positive and no imaging was performed, one did not want the metal plate removed at 18 months, and one converted to another treatment. As such, 17 HTO patients could be analyzed.

Table 1
Baseline parameters of the different patient groups.

Parameter mean ± SD or n (%)	KJD_{TKA} (n = 8)	KJD_{HTO} (n = 8)	HTO (n = 17)	p-value	OAI tibia (n = 32)	OAI femur (n = 32)
Age (years)	57.8 ± 6.3	50.9 ± 7.7	48.9 ± 6.3	**0.014**	64.9 ± 8.4	65.4 ± 8.5
BMI (kg/m^2)	26.9 ± 3.7	27.7 ± 3.9	26.7 ± 2.8	0.785	27.3 ± 3.9	27.6 ± 3.3
Male	4 (50)	6 (75)	12 (71)	0.530	12 (38)	8 (25)
Medial MAC	6 (75)	8 (100)	8 (100)	**0.034**	-	-
Kellgren-Lawrence				**0.002**		
	0 (0)	0 (0)	0 (0)		21 (66)	10 (31)
- Grade 0	0 (0)	1 (13)	2 (12)		4 (13)	15 (47)
- Grade 1	0 (0)	1 (13)	7 (41)		4 (13)	3 (9)
- Grade 2	3 (38)	6 (75)	7 (41)		3 (9)	4 (13)
- Grade 3	5 (63)	0 (0)	1 (4)		0 (0)	0 (0)
- Grade 4						
Baseline T2 relaxation times (ms)						
MAC tibia	48.1 (2.8)	47.4 (4.1)	47.9 (4.8)	0.932	41.8 (2.4)	-
LAC tibia	43.1 (2.3)	40.3 (3.2)	41.4 (3.5)	0.231		
MAC femur	55.0 (2.4)	53.7 (1.9)	54.9 (3.3)	0.571	-	51.8 (3.1)
LAC femur	52.8 (2.4)	52.0 (3.0)	53.4 (4.9)	0.778		
Baseline volumes (mm^3)						
MAC tibia	876 (285)	1496 (502)	1432 (466)	**0.011**	-	-
LAC tibia	1962 (632)	2074 (523)	2022 (282)	0.882		
MAC femur	2074 (289)	2967 (712)	2802 (636)	**0.010**		
LAC femur	3776 (1352)	3745 (774)	3463 (700)	0.646		

KJD_{TKA} = knee joint distraction (KJD) patients with indication total knee arthroplasty; KJD_{HTO} = KJD patients with indication high tibial osteotomy (HTO); MAC = most affected compartment; LAC = least affected compartment; OAI tibia = Osteoarthritis Initiative (OAI) patients matched with case-control matching for the tibia; OAI femur = OAI patients matched with case-control matching for the femur; SD = standard deviation. P-values are calculated between the three intervention groups with one-way ANOVA, with post-hoc Tukey HSD tests in case of statistical significance (bold p-values), which showed that all statistically significant differences were between KJD_{TKA} and HTO (age and medial MAC) or KJD_{TKA} and both other groups. There were no statistically significant differences between KJD_{HTO} and HTO.

The baseline characteristics of the three patient groups, as well as the femur-matched and tibia-matched OAI groups, are shown in Table 1. KJD_{TKA} patients had a higher age than HTO patients, and a higher KLG than KJD_{HTO} and HTO patients. There were no statistically significant differences between KJD_{HTO} and HTO. As such, when evaluating changes over time, the comparisons KJD_{TKA} and KJD_{HTO} were corrected for baseline KLG, while the comparisons between KJD_{HTO} and HTO were only corrected for corresponding baseline imaging values.

T2-mapping results after treatment

For both T2 relaxation times and volumes, ICC values showed good (all femur ICCs) or excellent (all tibia ICCs) agreement between the observers (supplementary table S1).

Baseline T2 times and volumes are shown in Table 1. There were no statistically significant differences between the groups in T2 times. The KJD_{TKA} group showed significantly lower volumes for the MAC tibia and femur than the KJD_{HTO} and HTO groups.

Changes in T2 relaxation time in the three separate groups are shown in Fig. 2 (baseline is set to 0). The KJD_{TKA} group did not show statistically significant changes over time (all $p > 0.1$), but did show a trend of a one-year increase followed by a slight decrease (for the MAC) or plateau (for the LAC) between one and two years. The KJD_{HTO} group showed an increase in T2 times, which was statistically significant for all regions (all $p < 0.025$) except the LAC femur ($p = 0.054$). HTO patients showed a significant T2 time increase in all regions (all $p < 0.006$). There were no significant differences between KJD_{TKA} and KJD_{HTO} or between KJD_{HTO} and HTO (all $p > 0.08$).

Changes in segmented cartilage volumes in the three groups are shown in Fig. 3 (baseline is set to 0). Only the KJD_{TKA} group showed significant volume increases in the MAC, statistically significant for the tibia ($p = 0.004$) but not the femur ($p = 0.052$). The other groups did not show clear volume changes (all $p \geq 0.1$). The changes in MAC tibia volume were significantly different between KJD_{TKA} and KJD_{HTO} ($p = 0.029$), but not when corrected for KLG ($p = 0.457$), which was significantly different between the two.

Pearson correlations between one- or two-year changes in T2 values and volumes were not statistically significant for any of the compartments or groups (all $p > 0.09$), except for the two-year LAC femur changes in the HTO group ($R = -0.660$; $p = 0.004$).

Pearson correlations between two-year changes in T2 values or volumes and clinical outcome (VAS pain) were not statistically significant for any compartment or patient group (all $p \geq 0.09$).

Influence of baseline characteristics

Combining the MAC and LAC, in the KJD_{TKA} group, only age had a significant positive effect on the change in T2 relaxation times in the tibia ($B = 0.310$, $p = 0.023$) and baseline T2 time had a significant negative effect on the change in the femur ($B = -0.629$, $p = 0.019$). In the KJD_{HTO} group, none of the baseline characteristics or T2 values had a statistically significant influence. In the HTO group, BMI ($B = -0.365$, $p = 0.002$) and baseline T2 time ($B = -0.234$, $p = 0.015$) had a significant negative effect on the change in the femur.

Comparison with osteoarthritis initiative

Regression analysis investigating the influence of baseline measures on cartilage T2 change were calculated from the (combined medial and lateral) femur and tibia using T2 times of 421 OAI participants that had at least two time points available. None of the patient characteristics had a significant influence on these changes over time, but baseline T2 times were negatively associated with the change in T2 times in the tibia ($B = -0.070$, $p = 0.001$) and femur ($B = -0.079$, $p < 0.001$), respectively. In all treated (KJD and HTO) patients together, only BMI ($B = -0.209$, $p = 0.029$) and baseline femur T2 times ($B = -0.330$, $p < 0.001$) had a significant influence on the change in femur T2 relaxation times. As such, case control matching between treated and untreated patients was based on baseline T2 values and BMI. For both the tibia and femur,

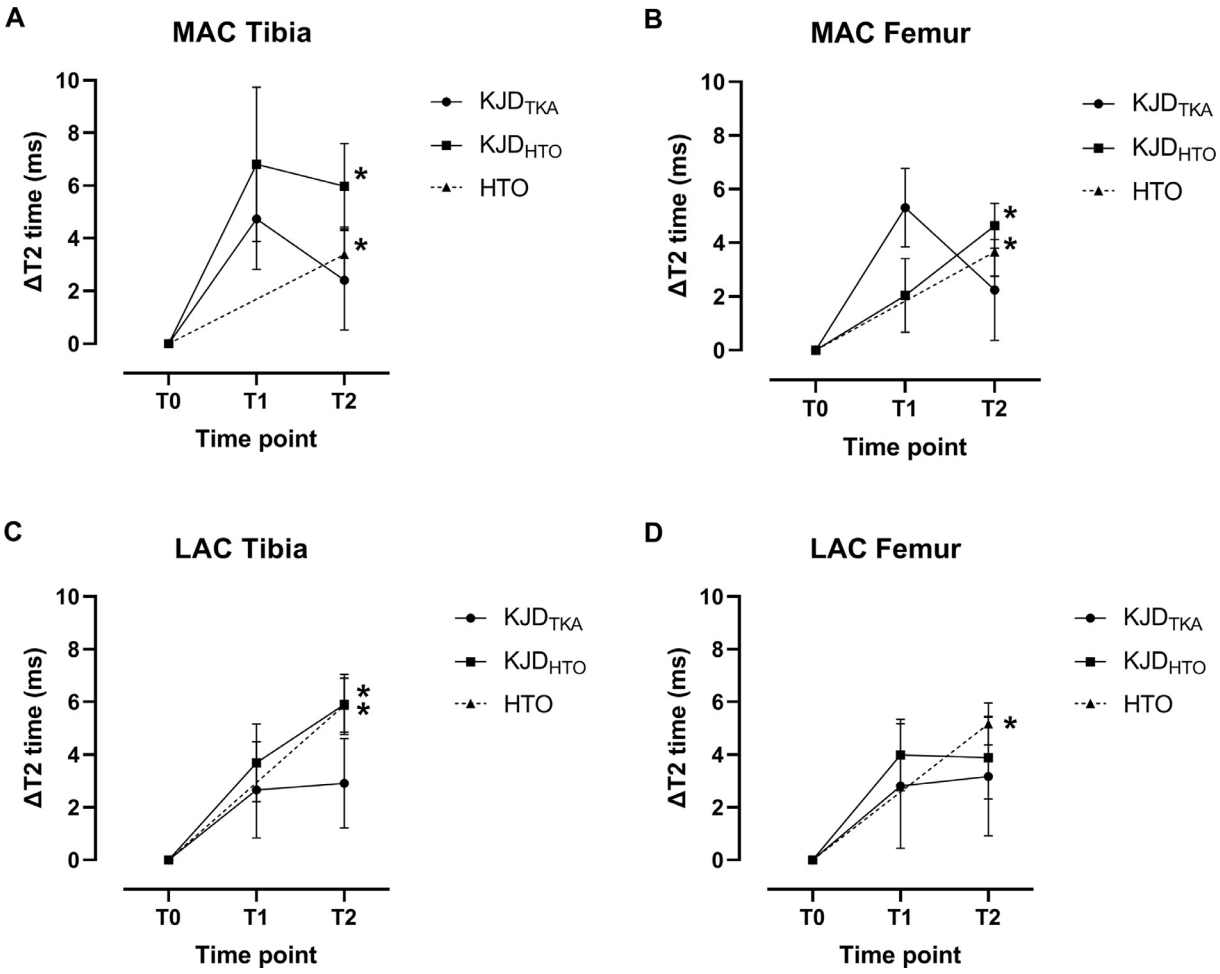

Fig. 2. Baseline-corrected T2 relaxation times for the three patient groups: patients indicated for total knee arthroplasty (TKA) and treated with knee joint distraction (KJD), patients indicated for high tibial osteotomy (HTO) and treated with KJD, and patients indicated for and treated with HTO. Changes are split per compartment: (A) the tibia of the most affected compartment (MAC); (B) the femur of the MAC; (C) the tibia of the least affected compartment (LAC); (D) the femur of the LAC. * indicates statistically significant changes ($p < 0.05$), for the KJD groups calculated with repeated measures ANOVA and for the HTO group calculated with paired t-tests.

tolerances of 4 ms and 5 kg/m^2 resulted in a match for all but one treated patient for tibia and femur. The progression of T2 values over time for these matched OAI patients is shown in Supplementary Figure S1.

Changes over time as represented by regression coefficients are shown for all treated (KJD and HTO) patients together and the matched OAI patients in Fig. 4. Treated patients showed an increase of 2.2 (95%CI 1.5–3.0) ms/year in the tibia and 2.1 (1.4–2.7) ms/year in the femur; Cartilage T2 in untreated OAI patients showed no change with 0.1 (-0.2–0.4) ms/year in the tibia and -0.1 (-0.8–0.7) ms/year in the femur.

For both the tibia and femur matched patients, patient age, baseline T2 relaxation time, sex, and KLG were statistically significantly different between the two groups (all $p < 0.03$). Corrected for these parameters, differences in T2 relaxation time changes were statistically significantly different between treated and untreated patients for the tibia ($p = 0.003$) and femur ($p < 0.001$).

Discussion

After treatment with KJD or HTO, an increase in cartilage T2 relaxation times was observed throughout the entire joint, similar between the two treatments and larger than could be expected as a result of natural OA progression alone. In TKA-indicated KJD patients the T2 value increase was not statistically significant.

An increase in T2 relaxation times can be the result of higher water concentration, lower collagen concentration, loss of collagen framework integrity, or a combination [9]. Remarkably, patients treated with KJD showed an initial T2 value increase in the first year after treatment, but a stabilization or even a decrease between one and two years post-treatment, especially in TKA-indicated patients. This might be a delayed effect of the six-week unloading in KJD treatment: articular cartilage may need loading for normal structuring of the collagen framework. A previous study applying T2-mapping of knee cartilage showed that 45 min of unloading (lying down) resulted in a T2 relaxation time increase (+0.9 ms), an effect that was even more pronounced in cartilage repair tissue (+4.3 ms) and the authors speculated it was the result of hydration and/or reorganization of the collagen organization [30]. As such, it is not unthinkable that six-week unloading may still show its effects on the collagen structure one year after treatment. Surprisingly, dGEMRIC analyses did not show significant changes over time in these patients, although HTO patients did show a trend of deterioration.

Systemic collagen type-II markers have previously been evaluated in multiple KJD cohorts, including the RCTs from which patients in the current study were included. Interestingly, all cohorts showed an initial decrease in net collagen type-II synthesis (i.e. more breakdown than synthesis), which gradually increased and at two years after treatment showed a significant increase in net collagen type-II synthesis [17,31]. This corresponds largely with the T2 relaxation times initially increasing

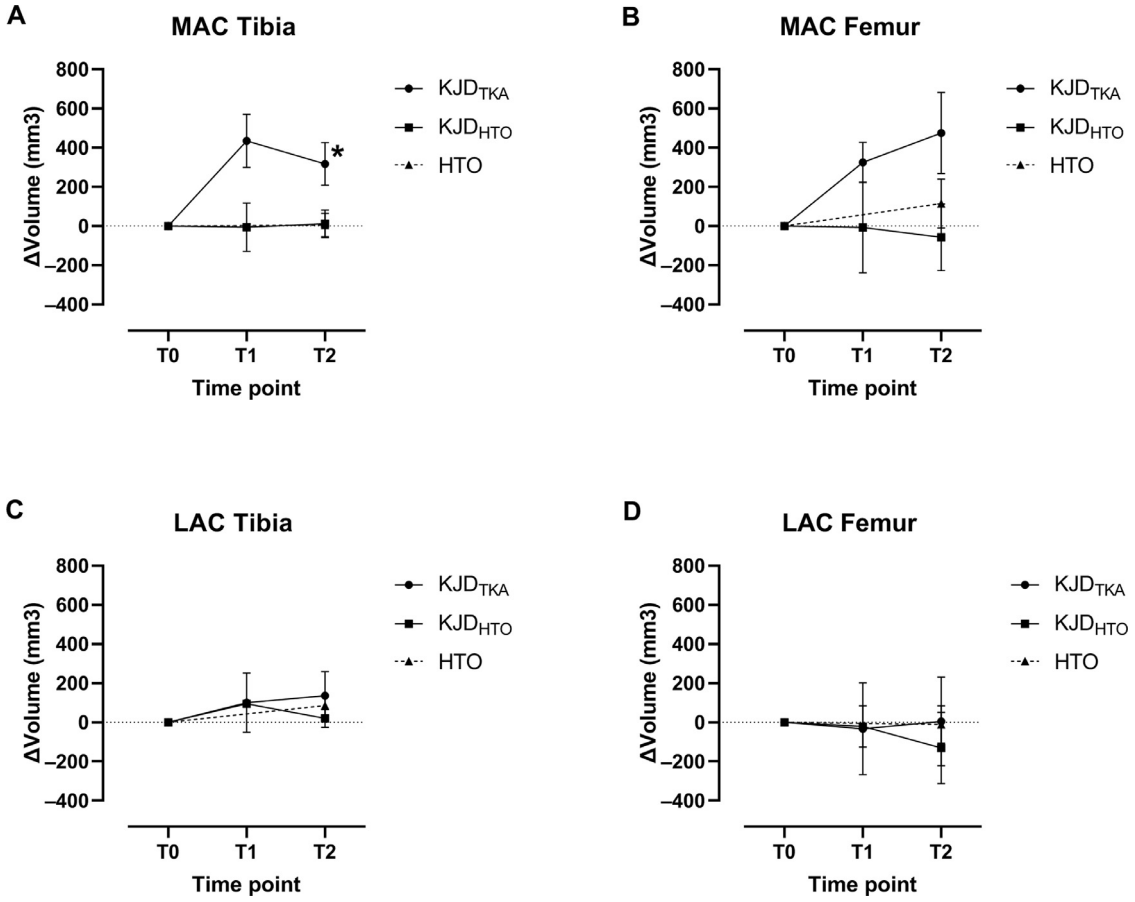

Fig. 3. Baseline-corrected segmented volumes for the three patient groups: patients indicated for total knee arthroplasty (TKA) and treated with knee joint distraction (KJD), patients indicated for high tibial osteotomy (HTO) and treated with KJD, and patients indicated for and treated with HTO. Changes are split per compartment: (A) the tibia of the most affected compartment (MAC); (B) the femur of the MAC; (C) the tibia of the least affected compartment (LAC); (D) the femur of the LAC. * indicates statistically significant changes ($p < 0.05$), for the KJD groups calculated with repeated measures ANOVA and for the HTO group calculated with paired t-tests.

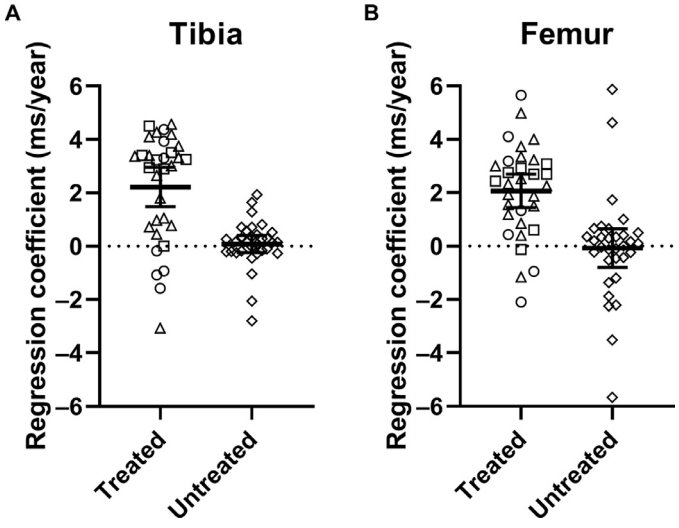

Fig. 4. T2 relaxation time changes for treated and untreated patients, expressed as regression coefficients (ms/year), for (A) the tibia and (B) the femur. Treated patients consisted of 32 patients treated with knee joint distraction (indicated for total knee arthroplasty (circles) or high tibial osteotomy (squares) or high tibial osteotomy (triangles); untreated patients consisted of 32 patients from the OsteoArthritis Initiative matched separately for the tibia and femur (diamonds), based on baseline T2 values and BMI.

and after one year decreasing, and suggests a short-term decrease in cartilage collagen content followed by a normalization after one year.

Only in TKA-indicated KJD patients, the increase in T2 relaxation times goes paired with a volume increase in the MAC. In a previous study optimized for cartilage thickness changes in patients from these RCTs, it was shown that KJD_{TKA} patients showed a significant increase in MAC cartilage thickness and decrease in denuded bone areas, indicating there is indeed new cartilage tissue formation [18]. The increase in T2 relaxation time could be the result of newly formed cartilage that needs time to mature. A T2-mapping study in children and adolescents showed that skeletal maturation in children caused a decrease in T2 relaxation times, potentially caused by increasing collagen content as a result of maturation [32]. Furthermore, T2-mapping studies in patients with a cartilage defect showed higher initial T2-values for repair cartilage compared to normal cartilage that decreased over time, and histological studies in dogs treated with KJD suggested a somewhat delayed normalization based on proteoglycan turnover [7,30,33,34]. Newly formed, young, repair cartilage that needs time to mature could explain the one-year T2 value increase and subsequent normalization that, at least in the MAC of TKA-indicated KJD patients, goes paired with an increase in cartilage volume. Alternatively, the collagen orientation of newly formed cartilage could be simply be similar to the more superficial tissue that had been lost before, as T2 values are short in the deep layer, where the collagen is oriented perpendicular to the subchondral bone, and longer in the superficial layer, where the collagen fibers are oriented more parallel to the cartilage surface [9]. Either way, while it is tempting to draw direct conclusion on paired T2 value and volume increases, it is impor-

tant to realize that the T2 values represent the entire cartilage and not just newly formed tissue.

In HTO-indicated KJD patients and HTO patients a significant increase in T2 values is seen, but no significant changes in cartilage volume, which corresponds with previous cartilage thickness results [18]. Although the increase in T2 values was significantly larger than in matched OAI patients, case-control matching between a late OA cohort (patients who need surgical treatment) and an early OA cohort (OAI) is not perfect, and the T2 value increase might still be the result of natural progression. Unfortunately, it is difficult to find a good control group and match patients on all patient characteristics, as the KJD and HTO patients have such far progressed OA that they require surgical intervention, and patients in that stage of the disease will not be followed in a cohort study for multiple years without any intervention. The fact that a higher age and BMI had a positive influence on the T2 value increase is consistent with other studies showing natural progression [10,35,36]. Also, in patients treated with an autologous chondrocyte transplantation for a cartilage defect, an increase in T2 values of 2.8 ms in a 1-2 year period was seen in the healthy (control) cartilage [7]. It might be that any surgical intervention, or a change in weight-bearing as a result, already affects cartilage content or structure, regardless of what intervention is performed. Still, while other studies have shown no change or a deterioration with respect to cartilage composition in the two years after HTO, this was the case only for dGEMRIC MRI [24,37,38]. Contrary to our findings, two studies evaluating T2 mapping up to one year after HTO or hemicallotasis osteotomy both showed a decrease in T2 values in the first year post-treatment [39,40]. Since in the current study no T2 mapping data was available shorter than two years after treatment, it might be that HTO patients showed an improvement in the first year and deterioration in the second, although this would indicate a pattern opposite to that seen in KJD patients. Alternatively, the patient populations of the other studies may have differed in parameters that were not evaluated but could be important, such as the posterior tibial slope that showed an association with T2 relaxation changes in one study [40].

The difference between the KJD groups is somewhat surprising. In the larger MRI cartilage thickness study in the original RCT, it was shown that mild OA patients (KLG $\leq$ 2) did not show significant changes in cartilage thickness or denuded bone areas, while severe OA patients (KLG $\geq$ 3) showed significant regeneration. In the current study, mild and severe OA could not be compared, since by this definition only two KJD patients in the current study had mild OA. The original indication of TKA or HTO might still reflect a difference in somewhat more or less severe OA, as indicated by the significant baseline difference in MAC cartilage volume as well. As such, the different responses in the two groups might be because more severely affected patients show a better response to KJD. Anecdotally, the two KJD patients with a KLG of 1 and 2 showed a higher than average T2 value increase combined with a much higher than average decrease in cartilage volume.

A clear limitation of this study was sample size. While it provides interesting exploratory results that despite the small sample size could reach statistical significance, and correspond well previous results, a larger sample size would likely allow for stronger conclusions. It would be worthwhile to perform imaging studies in a larger group of patients, either 3T T2-mapping or more advanced sequences on a 7T scanner, and add more time points, including a scan immediately post-treatment. HTO patients could be included as well, although that may require changes to the treatment protocol. Imaging studies could be combined with synovial biomarker analyses to better interpret imaging analysis results.

Another limitation of this study was that we could not separate deep and superficial cartilage, as is done often in T2-mapping studies. Many patients showed severely degenerated joints, especially in the MAC, that at times barely had cartilage left and as such did not allow for segmentation of different layers. Also, no unloading protocol before undergoing the MRI scans was used, so differences in pre-scan loading throughout the day, between patients or time points, might have influenced results. Monitoring physical activity in the period before each scan, and measuring potentially influencing patient characteristics such as BMI at all-time points, could be included for future research as well.

In conclusion, treatment with KJD or HTO results in an increase in T2 relaxation times, which could indicate a progressive loss or a reorganization of collagen structure integrity. In the most severe KJD patients with indication TKA, this increase seems limited to the first year after treatment, after which the relative collagen content and structure improves. This may partly be the result of maturation of newly formed cartilage, since part of the KJD patients show a significant cartilage volume increase as well, which fits previous biochemical markers studies and animal studies on KJD. Based on these results, KJD should be the preferred treatment for patients with bicompartmental or severe OA, while in case of mild unicompartmental (medial) OA both KJD and HTO could be considered.

Declaration of Competing Interest

W. Wirth is part-time employee and share-holder of Chondrometrics GmbH and received consulting fees from Galapagos N.V. The other authors declare no potential conflict of interest.

CRediT authorship contribution statement

M.P. Jansen: Conceptualization, Methodology, Formal analysis, Writing – original draft. **S.C. Mastbergen:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **W. Wirth:** Resources, Formal analysis, Writing – review & editing. **S. Spruijt:** Resources, Writing – review & editing. **R.J.H. Custers:** Resources, Writing – review & editing. **R.J. Van Heerwaarden:** Resources, Writing – review & editing. **F.P.J.G. Lafeber:** Conceptualization, Methodology, Formal analysis, Writing – review & editing.

Acknowledgements

The authors thank Nick Besselink (NB) and Chien Nguyen (CN) for their work segmenting the MRI scans. The authors acknowledge data collection and curation efforts from the OAI, a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) and funded by the NIH.

Role of the funding source

Parts of this study were funded by ZonMW (The Netherlands Organisation for Health Research and Development, project number 95110008) and ReumaNederland (Dutch Arthritis Society, project number LLP-9). The funders had no role in the study design, data collection, analysis or interpretation of the data, or in the writing of, or decision to submit the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ostima.2021.100004.

References

[1] J.A. Buckwalter, J.A. Martin, Osteoarthritis, Adv. Drug. Deliv. Rev. 58 (2006) 150–167, doi:10.1016/j.addr.2006.01.006.
[2] J.H. Kellgren, J.S. Lawrence, Radiological assessment of osteo-arthrosis, Ann. Rheum. Dis. 16 (1957) 494–502, doi:10.1136/ard.16.4.494.
[3] D.J. Hunter, A. Guermazi, G.H. Lo, et al., Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score), Osteoarthr. Cartil. 19 (2011) 990–1002, doi:10.1016/j.joca.2011.05.004.
[4] F. Eckstein, W. Wirth, Quantitative cartilage imaging in knee osteoarthritis, Arthritis 2011 (2011) 1–19, doi:10.1155/2011/475684.
[5] G.E. Gold, C.A. Chen, S. Koo, et al., Recent advances in MRI of articular cartilage, Am. J. Roentgenol. 193 (2009) 628–638, doi:10.2214/AJR.09.3042.

[6] S. Trattnig, T.C. Mamisch, K. Pinker, et al., Differentiating normal hyaline cartilage from post-surgical repair tissue using fast gradient echo imaging in delayed gadolinium-enhanced MRI (dGEMRIC) at 3 Tesla, Eur. Radiol. 18 (2008) 1251–1259, doi:10.1007/s00330-008-0859-3.

[7] G.H. Welsch, S. Trattnig, T. Hughes, et al., T2 and T2* mapping in patients after matrix-associated autologous chondrocyte transplantation: initial results on clinical use with 3.0-Tesla MRI, Eur. Radiol. 20 (2010) 1515–1523, doi:10.1007/s00330-009-1669-y.

[8] J.A. Choi, G.E. Gold, MR imaging of articular cartilage physiology, Magn. Reson. Imaging Clin. N. Am. 19 (2011) 249–282, doi:10.1016/j.mric.2011.02.010.

[9] T.J. Mosher, B.J. Dardzinski, Cartilage MRI T2 relaxation time mapping: Overview and applications, Semin. Musculoskelet. Radiol. 8 (2004) 355–368, doi:10.1055/s-2004-861764.

[10] T. Baum, G.B. Joseph, D.C. Karampinos, et al., Cartilage and meniscal T2 relaxation time as non-invasive biomarker for knee osteoarthritis and cartilage repair procedures, Osteoarthr. Cartil. 21 (2013) 1474–1484, doi:10.1016/j.joca.2013.07.012.

[11] B.S. Kester, P.M. Carpenter, H.J. Yu, et al., T1ρ/T2 mapping and histopathology of degenerative cartilage in advanced knee osteoarthritis, World J. Orthop. 8 (2017) 350–356, doi:10.5312/wjo.v8.i4.350.

[12] R. Stahl, G. Blumenkrantz, J. Carballido-Gamio, et al., MRI-derived T2 relaxation times and cartilage morphometry of the tibio-femoral joint in subjects with and without osteoarthritis during a 1-year follow-up, Osteoarthr. Cartil. 15 (2007) 1225–1234, doi:10.1016/j.joca.2007.04.018.

[13] E. David-Vaudey, S. Ghosh, M. Ries, S. Majumdar, T2 relaxation time measurements in osteoarthritis, Magn. Reson. Imaging 22 (2004) 673–682, doi:10.1016/j.mri.2004.01.071.

[14] A. Amendola, D.E. Bonasia, Results of high tibial osteotomy: review of the literature, Int. Orthop. 34 (2010) 155–160, doi:10.1007/s00264-009-0889-8.

[15] F. Intema, P.M. Van Roermund, A.C.A. Marijnissen, et al., Tissue structure modification in knee osteoarthritis by use of joint distraction: an open 1-year pilot study, Ann. Rheum. Dis. 70 (2011) 1441–1446, doi:10.1136/ard.2010.142364.

[16] J.A.D. van der Woude, K. Wiegant, R.J. van Heerwaarden, et al., Knee joint distraction compared with high tibial osteotomy: a randomized controlled trial, Knee Surg. Sport Traumatol. Arthrosc. 25 (2017) 876–886, doi:10.1007/s00167-016-4131-0.

[17] M.P. Jansen, N.J. Besselink, R.J. van Heerwaarden, et al., Knee joint distraction compared with high tibial osteotomy and total knee arthroplasty: two-year clinical, radiographic, and biochemical marker outcomes of two randomized controlled trials, Cartilage 12 (2019) 181–191, doi:10.1177/1947603519828432.

[18] M.P. Jansen, S. Maschek, R.J. van Heerwaarden, et al., Changes in cartilage thickness and denuded bone area after knee joint distraction and high tibial osteotomy - post-hoc analyses of two randomized controlled trials, J. Clin. Med. 10 (2021) 368, doi:10.3390/jcm10020368.

[19] A. Hoorntje, P. Kuijer, K.L.M. Koenraadt, et al., Return to sport and work after randomization for knee distraction versus high tibial osteotomy: is there a difference? J. Knee Surg. (2020), doi:10.1055/s-0040-1721027.

[20] M.P. Jansen, T. Boymans, R.J.H. Custers, et al., Knee Joint distraction as treatment for osteoarthritis results in clinical and structural benefit: a systematic review and meta-analysis of the limited number of studies and patients available, Cartilage 194760352094294 (2020), doi:10.1177/1947603520942945.

[21] W.H. Jung, R. Takeuchi, C.W. Chun, et al., Second-look arthroscopic assessment of cartilage regeneration after medial opening-wedge high tibial osteotomy, Arthrosc. - J. Arthrosc. Relat. Surg. 30 (2014) 72–79, doi:10.1016/j.arthro.2013.10.008.

[22] W.H. Jung, R. Takeuchi, C.W. Chun, et al., Comparison of results of medial opening-wedge high tibial osteotomy with and without subchondral drilling, Arthrosc. - J. Arthrosc. Relat. Surg. 31 (2015) 673–679, doi:10.1016/j.arthro.2014.11.035.

[23] M.P. Jansen, S.C. Mastbergen, J.W. MacKay, et al., Knee joint distraction results in MRI cartilage thickness increase up to ten years after treatment, Rheumatology (2021), doi:10.1093/rheumatology/keab456.

[24] N.J. Besselink, K.L. Vincken, L.W. Bartels, et al., Cartilage quality (dGEMRIC Index) following knee joint distraction or high tibial osteotomy, Cartilage 11 (2018) 19–31, doi:10.1177/1947603518777578.

[25] M.P. Jansen, S.C. Mastbergen, R.J.van Heerwaarden, et al., Knee joint distraction in regular care for treatment of knee osteoarthritis: a comparison with clinical trial data, PLoS One 15 (2020) e0227975, doi:10.1371/journal.pone.0227975.

[26] C.G. Peterfy, E. Schneider, M. Nevitt, The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee, Osteoarthr. Cartil. 16 (2008) 1433–1441.

[27] W. Wirth, S. Maschek, P. Beringer, F. Eckstein, Subregional laminar cartilage MR spin–spin relaxation times (T2) in osteoarthritic knees with and without medial femorotibial cartilage loss – data from the Osteoarthritis Initiative (OAI), Osteoarthr. Cartil. 25 (2017) 1313–1323, doi:10.1016/j.joca.2017.03.013.

[28] W. Wirth, S. Maschek, F.W. Roemer, et al., Radiographically normal knees with contralateral joint space narrowing display greater change in cartilage transverse relaxation time than those with normal contralateral knees: a model of early OA? – data from the Osteoarthritis Initiative (OAI), Osteoarthr. Cartil. 27 (2019) 1663–1668, doi:10.1016/j.joca.2019.06.013.

[29] T.K. Koo, M.Y. Li, A guideline of selecting and reporting intraclass correlation coefficients for reliability research, J. Chiropr. Med. 15 (2016) 155, doi:10.1016/J.JCM.2016.02.012.

[30] T.C. Mamisch, S. Trattnig, S. Quirbach, et al., Quantitative T2 mapping of knee cartilage: Differentiation of healthy control cartilage and cartilage repair tissue in the knee with unloading - Initial results, Radiology 254 (2010) 818–826, doi:10.1148/radiol.09090335.

[31] K. Wiegant, P.M. van Roermund, F. Intema, et al., Sustained clinical and structural benefit after joint distraction in the treatment of severe knee osteoarthritis, Osteoarthr. Cartil. 21 (2013) 1660–1667, doi:10.1016/j.joca.2013.08.006.

[32] H.K. Kim, S. Shiraj, C.G. Anton, et al., Age and sex dependency of cartilage T2 relaxation time mapping in MRI of children and adolescents, Am. J. Roentgenol. 202 (2014) 626–632, doi:10.2214/AJR.13.11327.

[33] A.A. Van Valburg, P.M. Van Roermund, A.C.A. Marijnissen, et al., Joint distraction in treatment of osteoarthritis (II): effects on cartilage in a canine model, Osteoarthr. Cartil. 8 (2000) 1–8, doi:10.1053/joca.1999.0263.

[34] K. Wiegant, F. Intema, P.M. Roermund, et al., Evidence of cartilage repair by joint distraction in a canine model of osteoarthritis, Arthritis Rheumatol. 67 (2015) 465–474, doi:10.1002/art.38906.

[35] T. Baum, G.B. Joseph, L. Nardo, et al., Correlation of magnetic resonance imaging-based knee cartilage T2 measurements and focal knee lesions with body mass index: thirty-six-month followup data from a longitudinal, observational multicenter study, Arthritis Care Res. (Hoboken) 65 (2013) 23–33, doi:10.1002/acr.21741.

[36] T.J. Mosher, Y. Liu, Q.X. Yang, et al., Age dependency of cartilage magnetic resonance imaging T2 relaxation times in asymptomatic women, Arthritis Rheum. 50 (2004) 2820–2828, doi:10.1002/art.20473.

[37] D.A. Parker, K.T. Beatty, B. Giuffre, et al., Articular cartilage changes in patients with osteoarthritis after osteotomy, Am. J. Sports Med. 39 (2011) 1039–1045, doi:10.1177/0363546510392702.

[38] M. Rutgers, L.W. Bartels, A.I. Tsuchida, et al., DGEMRIC as a tool for measuring changes in cartilage quality following high tibial osteotomy: a feasibility study, Osteoarthr. Cartil. 20 (2012) 1134–1141, doi:10.1016/j.joca.2012.07.001.

[39] H. Nishioka, E. Nakamura, J. Hirose, et al., MRI T1ρ and T2 mapping for the assessment of articular cartilage changes in patients with medial knee osteoarthritis after hemicallotasis osteotomy, Bone Jt. Res. 5 (2016) 294–300, doi:10.1302/2046-3758.57.BJR-2016-0057.R1.

[40] Atkinson H.F., Birmingham T.B., Schulz J.M., et al (2021) High tibial osteotomy to neutral alignment improves medial knee articular cartilage composition. Knee Surg. Sport Traumatol. Arthrosc. 1–10. https://doi.org/10.1007/s00167-021-06516-9