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The degeneration and destruction of femoral articular cartilage shows a greater degree of deterioration than that of the tibial and patellar articular cartilage in early stage knee osteoarthritis: a cross-sectional study

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SUMMARY

Objective: The aim of the present study was to examine whether the degenerative and morphological changes of articular cartilage in early stage knee osteoarthritis (OA) occurred equally for both femoral- and tibial- or patellar- articular cartilage using magnetic resonance imaging (MRI)-based analyses.
Design: This cross-sectional study was approved by the ethics committee of our university. Fifty patients with early stage painful knee OA were enrolled. The patients underwent 3.0 T MRI on the affected knee joint. Healthy volunteers who did not show MRI-based OA changes were also recruited as controls ($n = 19$). The degenerative changes of the articular cartilage were quantified by a T2 mapping analysis, and any structural changes were conducted using Whole Organ Magnetic Resonance Imaging Score (WORMS) technique.
Results: All patients showed MRI-detected OA morphological changes. The T2 values of femoral condyle (FC) ($P < 0.0001$) and groove ($P = 0.0001$) in patients with early stage knee OA were significantly increased in comparison to those in the control, while no significant differences in the T2 values of patellar and tibial plateau (TP) were observed between the patients and the control. The WORMS cartilage and osteophyte scores of the femoral articular cartilage were significantly higher than those in the patellar- ($P = 0.001$ and $P = 0.007$, respectively) and tibial- ($P = 0.0001$ and $P < 0.0001$, respectively) articular cartilage in the patients with early stage knee OA.
Conclusions: The degradation and destruction of the femoral articular cartilage demonstrated a greater degree of deterioration than those of the tibial- and patellar- articular cartilage in patients with early stage knee OA.

Introduction

Osteoarthritis (OA) is an age-related progressive joint disease, which induces pain, significant functional impairment, a loss of mobility and a diminished activity in daily life[1,2]. As the prevalence of this disease is gradually increasing due to the increasing longevity of the population, OA is therefore now becoming an important public health concern[3]. As there are no current interventions proven to restore cartilage or curtail the disease processes, and we cannot inhibit the progression of this disease by any methods, such as medication, the only treatment methods currently available for knee OA is symptom-modifying treatment, while no disease-modifying treatment yet exists for knee OA[4].

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OA is primarily induced by the degeneration of articular cartilage, which is initiated by a loss of proteoglycan (PG) and an increase in water content, followed by a loss of type II collagen and a change in collagen fiber orientation. The progressive loss of hyaline cartilage is one of the hallmark of the destruction of OA. The subchondral bone and synovium, in addition to articular cartilage, are also involved in this aspect of OA progression, although the changes of these tissues are considered to be a secondary phenomenon that is induced by the primary changes[5,6]. There are many problems that must be overcome before any significant breakthroughs can be achieved in this field. First, the disease mechanisms of OA will have to be better understood in order to identify the best targets for initiating treatments in preclinical and clinical trials. The stage- and site-specific OA pathophysiological events may make the elucidation of the disease mechanisms difficult. Second, patients tend to show various rates of disease progression, so we must be able to predict which patients will progress to OA over time, and identify whether these patients have any distinguishing features based on clinical, radiological, or laboratory assessments. Third, once potentially disease-modifying treatments become available, then determining the efficacy of such intervention will be important. Therefore, it is widely agreed that the validation of improved imaging and chemical biomarkers may make it possible to circumvent some of these problems[7,8].

Precisely how this disease progresses in patients with knee OA still remains unclear. For example, it is uncertain whether the degeneration and destruction of articular cartilage occurs simultaneously in the femoral, tibial and patellar articular cartilage, or if some spatial and temporal difference exists in the degeneration and destruction of articular cartilage. Magnetic resonance imaging (MRI) is more sensitive than radiography to detect bone and soft tissue changes, which are features of OA[9]. In early stage of knee OA, OA changes begin at the molecular level of the articular cartilage, such as a loss of PG, an increased water content, and the disorganization of the collagen network, probably before any morphologic changes take place in the articular cartilage. The morphologic changes, such as cartilage lesion, bone attritions, cysts, bone marrow abnormalities (BMAs), osteophyte, meniscal pathology, synovitis and ligament changes, can be visualized and semi-quantified by MRI. T2 mapping sequence on MRI is a technique that can sensitively detect early biochemical changes in the water content and any disorganization of the collagen network in articular cartilage. In addition, we can also evaluate the OA-induced structural joint changes semi-quantitatively by, for instance, using the Whole Organ Magnetic Resonance Imaging Score (WORMS). These techniques may enable us to further understand the very early stage of knee OA.

In this cross-sectional study, the aim of the present study was to examine whether the degenerative and morphological changes of articular cartilage in early stage knee OA occurred equally between the femoral- and the tibial- or patellar- articular cartilage using an MRI-based T2 mapping analysis and the WORMS technique.

Methods

Subjects and methods

This cross-sectional study was approved by the ethics committee of our university. Patients who first visited the outpatient clinic at our university hospital to seek therapy for knee pain due to OA were asked to participate in the study. All patients who agreed to participate provided their written informed consent before enrollment in this study. All patients had medial knee OA and underwent the initial medical examination at our outpatient clinic between May 2012 and December 2012. The patients included in this analysis were determined based on the conditions described below. The sample size of this study was determined based on the number of patients who demonstrated all of these conditions during the study period.

The diagnosis of knee OA was established according to the American College of Rheumatology criteria[10]. The inclusion criteria for the present study were (1) subjects who were able to walk without walking aids and fulfilled the criteria for knee OA of the medial femoro-tibial joint, (2) subjects who were at least 40 years old, but less than 80 years old, and (3) all subjects had radiographic knee OA with Kellgren–Lawrence (K/L) grade 2 or less as evaluated by weight-bearing antero-posterior X-rays of the tibio-femoral joint (TFJ) using the bilateral standing extended view[11,12]. The exclusion criteria included (1) patients who had received drugs for knee OA (oral [e.g., non-steroidal anti-inflammatory drugs (NSAIDs) and opioid] or intra-articular injection [e.g., hyaluronic acid and corticosteroids]) prescribed by physicians in the previous 3 months, (2) those who had RA or arthritis due to infection or injury, (3) patients who had undergone joint replacement surgery, (4) patients who had secondary knee OA, (5) patients with patello-femoral OA with a K/L grade of 3 or higher, (6) patients with severe OA (K/L grade 3 or higher) in their hip joint and (7) patients who had a valgus knee [femoro-tibial angle (FTA); $<174^\circ$].

As the T2 values of articular cartilage are known to be affected by artifacts, such as the magic angle effect (MAE), healthy volunteers without MRI-based OA changes were recruited and the T2 values were also evaluated (Supplemental Table 1) (Non-knee OA control, Table II)[13]. The healthy volunteers included subjects in their twenties with no history of knee joint injury or knee pain recruited from our university. Although 20 healthy volunteers were originally recruited, one subject was excluded due to the detection of MRI-based OA changes; therefore, the remaining 19 healthy volunteers were included in this study.

Radiographic evaluation of knee OA

The standing, extended and antero-posterior and lateral view radiographs were taken at the first visit to the hospital according to the previously reported[12,14]. The joint space width (JSW) was determined at the center point of the medial femoro-tibial compartment on a radiograph using a 0.1-mm graduated magnifying lens[12,15,16]. The FTA was measured using goniometer on standing, as well as extended and antero-posterior view radiographs. All radiographs were quantified independently by two readers (SH and RS) who were blinded to the baseline characteristics of the patients.

MRI-based evaluation of knee OA

All patients showed either K/L grade 0, 1 or 2, and were also examined with the MAGNETOM Symphony syngo MR 3.0-Tesla MRI system (Siemens Medical Solutions, Erlangen, Germany) using sagittal and coronal two-dimensional (2D) fat-suppressed (FS) and T2-weighted image fast spin-echo (FSE) sequences (TR: 5000 ms, TE: 70 ms, FOV:160 mm, matrix: 384 × 307, slice thickness: 3 mm, turbo-factor: 17, flip-angle: 150, scan time: 3′00″) with

Table I
Patient characteristics

n	50
Age (years)	57 (15.1)
BMI (kg/cm^2)	24.1 (3.9)
Gender (M/F)	23/27
K/L grade (0/1: 2)	30 (60%): 20 (40%)
FTA (°)	178.4 (2.6)
JSW (medial/lateral) (mm)	3.7 (0.9)/4.7 (1.0)

The data are the means (S.D.).

Table II
T2 values of the articular cartilage in both the non-knee OA controls and the patients with early stage knee OA

	Division	Non-knee OA control	Early stage knee OA	*P*
PFJ	G	41.5 (3.5)	46.2 (4.4)	<0.0001
	P	36.3 (4.9)	33.4 (4.5)	0.024
	P	<0.0001	<0.0001	
	Δ(G−P)	5.2 (5.2)	12.8 (4.6)	0.001
	MFa	42.1 (5.4)	48.5 (6.1)	<0.0001
	MP	36.7 (5.8)	34.7 (6.3)	0.235
	P	0.005	<0.0001	
	Δ(MFa−MP)	5.4 (7.2)	13.8 (7.9)	<0.0001
	LFa	40.9 (5.0)	44.0 (5.9)	0.046
	LP	35.9 (5.7)	32.9 (5.1)	0.037
	P	0.012	<0.0001	
	Δ(LFa−LP)	5.0 (7.6)	11.1 (6.4)	0.001
TFJ	FC	38.4 (3.8)	41.2 (3.3)	0.013
	TP	33.0 (4.5)	32.3 (3.1)	0.449
	P	<0.0001	<0.0001	
	Δ(FC−TP)	5.4 (3.2)	8.9 (3.2)	<0.0001
	MFC	39.2 (4.2)	41.7 (3.6)	0.020
	MTP	33.8 (5.1)	33.6 (3.8)	0.826
	P	<0.0001	<0.0001	
	Δ(MFC−MTP)	5.4 (4.1)	8.1 (3.8)	0.012
	LFC	38.4 (4.1)	40.7 (4.0)	0.039
	LTP	32.3 (4.4)	31.1 (3.4)	0.225
	P	<0.0001	<0.0001	
	Δ(LFC−LTP)	6.1 (4.0)	9.7 (4.3)	0.003

Data indicates mean (SD).G: groove, P: patellar articular surface,

an 8-channel integrated Parallel Acquisition Technique (iPAT) knee coil. A positioning device for the ankle and knee was used to ensure uniformity between the patients. The diagnosis of knee OA for the subjects was made using the 3 T MRI findings according to the previously reported method[13]. The compartments of the knee joint were divided into 14 subdivisions; three regions [anterior (a), central (b), and posterior (c)] of the medial and lateral femur (MF and LF) and tibial plateaus (MTP and LTP), and two regions (medial and lateral) of the patella (MP and LP) (Fig. 1)[17]. To conduct the present study, we defined that the femoral groove articular surface (G), which consists of MFa and LFa, comes in contact with the patellar articular surface (P), which consists of MP and LP, and the femoral condyle (FC) articular surface, which consists of MFc, MFp, LFc and LFp, comes in contact with the tibial plateau (TP) articular surface, which consists of MTa, MTc, MTp, LTa, LTc and LTp. The medial femoral condyle (MFC) consists of MFc and MFp, while the lateral femoral condyle (LFC) consists of LFc and LFp.

T2 mapping

T2 values were obtained from T2 mapping, which were calculated from a five multi-echo, spin-echo (MESE) sequence (TR: 1000 ms, TE: 13.8, 27.6, 41.4, 55.2 and 69.0 ms, slice thickness: 3 mm, FOV: 160 mm, matrix: 384 × 384, scan time: 3′30″) and a linear curve fitting method was used. The regions of interest (ROIs) on T2 mapping were manually drawn by one operator (SH) using a three-dimensional image analysis software program (Virtual Place Liberty Lite; AZE, Tokyo, Japan) and excluded any artifacts, fluid, and subchondral bone from ROIs. In the patients, a ROIs analysis was performed on five consecutive slices and the mean T2 values were calculated through the five slices for each subdivisions.

WORMS scoring

The OA morphologic changes, such as cartilage lesion, bone attritions, cysts, BMAs, osteophyte, meniscal pathology, synovitis and ligament changes were scored using the WORMS criteria. Each region of a compartment surface received its own score, followed by the method reported previously[17]. At each region, the cartilage morphology was scored 0–6. The subarticular BMAs and bone cysts were each scored 0–3. The subchondral bone attrition was scored 0–3. Osteophytes were scored 0–7. The anterior and posterior cruciate ligaments (ACL and PCL) were scored 0 or 1. The medial and lateral collateral ligaments (MCL and LCL) were scored 0, 1 and 2. The anterior horn, posterior horn, and body of the medial and lateral meniscus were each scored and added together to total a score of 0–6. No intravenous contrast was injected in this study, which thus precluded us from differentiating synovial thickening and joint effusion. Thickening and effusion were therefore graded collectively as per the WORMS protocol from 0–3[17].

Reproducibility measurements

The intra-observer reproducibility (SH) of the radiographic grading of OA was measured at separate times for twenty patients [interclass correlation coefficient (ICC) 0.97 (95% confidence interval (CI): 0.90–0.99)]. The inter-observer reproducibility was measured by two observers (SH and RS) who conducted 20 examinations [ICC 0.93 (95% CI: 0.81–0.96)].

The intra-observer reproducibility (SH) of both the T2 value measurement and the WORMS evaluation by MRI measured twice for ten sections was high [Inter-reader agreement (ICC) 0.91 (95% CI 0.84–0.98) for T2 value, 0.90 (95% CI 0.45–0.98) for WORMS, respectively]. Two observers (SH and MK) conducted all ten examinations in order to assess the inter-observer reproducibility. They were blinded to any patient information during the evaluation process. The inter-observer reproducibility was also high [ICC: 0.87 (95% CI 0.79–0.92) for T2 value measurement, 0.91 (95% CI 0.49–0.98) for WORMS].

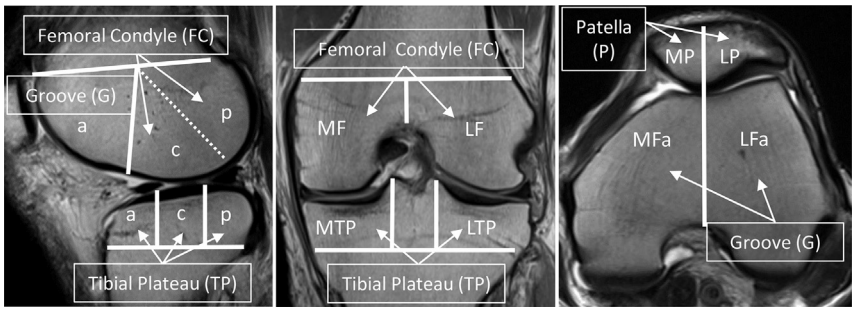

Fig. 1. Fourteen subdivisions of the knee joint evaluated in the study. The compartments of the knee joint were divided into 14 subdivisions, as defined in WORMS. The femoral groove articular surface (G), which consists of medial and lateral anterior condyles (MFa and LFa), comes in contact with the patellar articular surface (P), which consists of medial facet (MP) and lateral facet (LP). The FC articular surface, which consists of medial and lateral, central and posterior femoral condyles (MFc, MFp, LFc and LFp), comes in contact with the TP articular surface, which consists of medial and lateral, anterior, central and posterior tibial plateau (MTa, MTc, MTp, LTa, LTc and LTp).

Data analysis

The paired *t*-test was used to compare either T2 values or WORMS scores between femoral articular cartilage and either the confronting tibial or patellar articular cartilage. The odds ratios (ORs) for whether the WORMS cartilage- and osteophyte- scores of the femoral components were higher than those of the tibial or patellar components were also calculated. A P-value < 0.05 was considered to be statistically significant. All analyses were performed using the SPSS 19.0 software program (SPSS Institute, Chicago, IL, USA).

Results

Patient characteristics

Fifty-six patients were initially enrolled. As six of the fifty-six patients (10.7%) were excluded since they did not meet the study criteria, the remaining 50 patients were included in the data analysis.

The patients were 57 years old age on average, and there was a slight female dominance (54%) (Table I). Thirty of the fifty patients (60%) showed radiographic OA severities of K/L grade 0/1, while the remaining twenty patients (40%) showed radiographic OA severities of K/L grade 2. No significant differences in the FTA and body mass index (BMI) were observed between the patients with K/L grades 0/1 and those with K/L grades 2 (KL0/1; 178.6°, KL2; 178.1°, $P = 0.561$ for FTA and KL0/1; 25.0 kg/m^2, KL2; 23.5 kg/m^2, $P = 0.19$ for BMI).

Comparison of the T2 values between the femoral- and the either tibilar- articular cartilage in the femoro-tibial joint (FTJ) or the patellar-articular cartilage in the pattelo-femoral joint (PFJ)

The degenerative changes in the articular cartilage in patients with early stage knee OA were evaluated by T2 mapping, and the T2 values in femoral articular cartilage were compared with those in either tibial- or patellar- articular cartilage. The T2 values in femoral articular cartilage (G and FC) were significantly higher in comparison to those in both patellar- (P) and tibial- (TP) articular cartilage in not only the patients with early stage knee OA but also in the control (Table II). However, in the PFJ, the T2 values of G in patients with early stage knee OA were significantly increased in comparison to those of G in the control, while the T2 values of P in patients were significantly decreased in comparison to those of P in the control (Table II). Similarly, in the TFJ, the T2 values in the FC in patients with early stage knee OA were significantly increased in comparison to those in control, while no significant differences in the T2 values of TP were observed between the patients and the control (Table II). The differences in the T2 values between femoral articular cartilage and both patellar (ΔG−P) and tibial articular cartilage (ΔFC−TP) in patients with early stage knee OA were significantly increased in comparison to those in the control (Table II). When PFJ and TFJ were further divided into two sub-groups (MFa and MP and LFa and LP for PFJ, MFC and MTP and LFC and LTP for TFJ), the same phenomenon regarding the differences in the T2 values was observed (Table II).

Comparison of WORMS scores between the femoral articular cartilage and the either tibial articular cartilage in the FTJ or the patellar articular cartilage in the PFJ

The morphological changes in the joint in patients with early stage knee OA were evaluated by WORMS. Among the eight established pathological changes associated with OA, both cartilage lesions and osteophytes were observed in all patients evaluated in the study (Table III), the pathological severity of these two changes were compared between the femoral- and the patellar- or tibial- articular cartilage. The WORMS cartilage scores of the femoral articular cartilage were significantly higher than those in the patellar- and tibial- articular cartilage (Table IV). When the PFJ and TFJ were further divided into two sub-groups in terms of the medial and lateral compartments in the knee joint, these phenomena of the WORMS cartilage scores were observed in the medial side of PFJ and on both sides of TFJ (Table IV). The OR for higher WORMS cartilage scores of femoral articular cartilage than those of the patellar articular cartilage in the patients was 2.1 (1.1–3.9, $P = 0.013$). The OR for higher WORMS cartilage scores of femoral articular cartilage than those of the tibial articular cartilage in the patients was 3.6 (95% CI; 1.8–6.9, $P < 0.0001$).

The WORMS osteophyte scores of the femoral articular cartilage were significantly higher than those of the both the patellar- and tibial- articular cartilage (Table IV). When the PFJ and TFJ were further divided into two sub-groups in terms of the medial and lateral compartments in the knee joint, these phenomena of the WORMS osteophyte scores were observed in the medial side of the PFJ and on both sides of TFJ (Table IV). No significant differences in the WORMS osteophyte scores were observed between the femoral- and the confronting patellar- articular cartilage in the patients [OR: 1.5 (0.9–2.6), $P = 0.16$]. The OR for higher WORMS osteophyte scores of the femoral articular cartilage than that of the tibial articular cartilage in the patients was 1.9 (1.0–3.5, $P = 0.026$).

Table III
The frequencies of the MRI-detected structural changes in the knee joint of the patients with early stage knee OA

	Frequency (%)
Cartilage lesion	100
BMAs	66.0
Bone cysts	58.0
Bone attrition	82.0
Osteophytes	100
Meniscal pathology	80.0
Synovitis	82.0
Ligaments	4.0

Table IV
A comparison of the WORMS score for the femoral and tibial articular cartilage in patients with early stage knee OA

	Division	WORMS	
		Cartilage lesion	Osteophytes
PFJ	G	2.8 (0.9)	1.8 (1.2)
	P	2.0 (1.5)	1.2 (1.3)
	P	0.001	0.007
	MFa	3.3 (1.3)	2.1 (1.3)
	MP	2.1 (1.7)	1.2 (1.3)
	P	<0.0001	<0.0001
	LFa	2.4 (1.2)	1.5 (1.5)
	LP	1.9 (1.7)	1.2 (1.5)
	P	0.056	0.154
TFJ	FC	2.5 (1.0)	1.2 (1.1)
	TP	1.7 (1.3)	0.6 (0.8)
	P	<0.0001	<0.0001
	MFC	2.8 (1.3)	1.1 (1.3)
	MTP	2.1 (1.5)	0.8 (0.9)
	P	<0.0001	0.012
	LFC	2.3 (1.2)	1.4 (1.4)
	LTP	1.5 (1.4)	0.6 (0.8)
	P	<0.0001	<0.0001

Discussion

The present study has revealed, for the first time, that the degenerative changes, detected by T2 mapping on MRI, and the morphological changes, detected by a WORMS analysis on MRI, of the femoral articular cartilage showed a greater degree of deterioration than those of both the tibial- and patellar- articular cartilage in the patients with early stage knee OA. This is considered to be unique and important information for obtaining a better understanding the disease processes, which has never previously been elucidated using classical radiographs.

To non-invasively and precisely monitor the degenerative changes of articular cartilage induced by OA, T2 mapping is a promising method for evaluation of articular cartilage, although some controversy still exists[18]. Alterations in the T2 values have been shown to correlate with changes in the water content, as well as the collagen structure and organization, which are associated with changes in the articular cartilage and its degradation. The best approach to evaluate OA has been suggested to be a combination of high resolution morphological images and biochemical MRI techniques[19], T2 mapping technology using 3 T MRI enabled us to obtain the results of the present study. To begin with, we need to confirm whether there are any degenerative and morphological differences in the normal articular cartilage between the femora and tibiae. Although the T2 values of articular cartilage were found to increase due to the progression of knee OA[20], only slight differences in the T2 values of the femoral articular cartilage were observed in comparison to those of the tibial articular cartilage in healthy subjects[21]. Therefore, the phenomena observed in the current study are therefore considered to be related to those that occur due to knee OA.

It is well known that the signal intensity of the short TE sequence changes as a result of increasing T2 values if the angle between the main magnetic field (B0) direction and the collagen fiber increases from 0°[22]. This is an artifact that is called MAE, and can occur in any tissue that contains anisotropically arranged collagen fibers, such as hyaline cartilage and meniscus. The T2 values are at their maximum at an angle of almost fifty-five degrees relative to B0[23]. The increased signal intensity in the articular cartilage created by MAE should not be confused with early degenerative changes in the cartilage substances[23]. We evaluated the T2 values of the femoral and tibial articular cartilage in healthy volunteers who did not show MRI-based OA changes, in addition to the patients with early stage knee OA, and found that there were differences in the T2 values between the femoral and tibial articular cartilage.

A previous study using 3.0 T MRI reported by Eckstein *et al.* measured the thickness of both the femoral- and tibial- articular cartilage[24]. Although no statistical analysis was conducted, the loss of the medial femoral articular cartilage was greater than that of the medial tibial articular cartilage in patients with K/L grade 2 and 3. In addition, the central subregions of both the medial femoral- and tibial- articular cartilage showed a greater degree of deterioration than the other subregions in these patients[24]. The results of that study are thus considered to support those of the current study.

In the initial phase of OA, morphologic changes of the articular cartilage usually occur after the biochemical alterations of the extracellular matrix. The highly structured collagen fibers become loosened by the degeneration of the articular cartilage and then transform into a random configuration. Structural changes of the cartilage matrix result in increased tissue stiffness, increased permeability and damage to the surrounding tissues. These alterations include a progressive increase in the subchondral plate thickness, alterations in the architecture of the subchondral trabecular bone and the formation of new bone at the joint margins (osteophytes), which is associated with vascular invasion of the calcified cartilage. These biomechanical changes to the joint also induce histological changes due to bone remodeling and, subsequently, induce structural joint changes[25].

The present study elucidated the spatial differences in the degenerative and structural articular cartilage changes in both FTJ and PFJ. Two possible reasons for this have been speculated. One is due to the difference in the articular cartilage thickness between the femur and tibia or patella. In cadaveric studies, the femoral articular cartilage was thinner than the tibial and patellar articular cartilage. The thickness of the femoral articular cartilage was 2.5 mm on average, while that of the patellar articular cartilage was 4.5 mm on average[25]. A similar result was shown in a study of a younger population (30 years of age on average)[26]. Another possibility, which is supported by the findings of several studies, is described below. The tibial cartilage deformation was observed with MRI and found to be significantly higher than that of the femoral cartilage after impact loading exercise (jumping from 40 cm height)[27]. The cartilage deformations by the compression and shear mechanical stresses were asymmetric between the femoral- and tibial- articular cartilage findings observed in a cadaveric study. The deformation ability of the tibial articular cartilage was markedly higher than that of the femoral articular cartilage[20]. A cadaveric study utilized a micro-scale cartilage-on-cartilage testing system to elucidate cartilage strain during femoral-tibial articulation as well as the mechanical properties of the femoral and tibial articular cartilages, and, as a result, the femoral articular cartilage was found to be stiffer in compression and shear than the tibial articular cartilage[28]. The mechanical stress to the cells regulates, in part, the cell metabolism and matrix synthesis. Differences in cell deformation in response to mechanical stress may therefore reflect differences in the cell characteristics, which maintain homeostasis by regulating the metabolic and cellular responses[28]. These microenvironmental cellar and molecular changes in the articular cartilage may thus later lead to OA changes in the joint. Although various mechanisms may play a role in such changes, these previous studies suggest that the femoral articular cartilage may be thinner and more fragile in response to mechanical stress than both tibial- and patellar- articular cartilage.

Age is a recognized risk factor for the development of OA, and there are age-dependent differences in both the morphology and T2 values of the patellar articular cartilage in asymptomatic females[29]. In the current study, the healthy control subjects included relatively young (twenties) individuals compared to the OA patients in order to account for the MAE of the femoral articular cartilage. Therefore, although there may be age-dependent differences in the T2 values of the articular cartilage, the current study focused on whether degenerative and/or morphological changes occur equally between the femoral and tibial or patellar articular cartilage in the setting of early stage knee OA. Therefore, the "healthy" control group was selected from the relatively young population "with healthy cartilage" in the current study.

The current study is associated with some limitations. Extended view radiographs were used to evaluate the severity of OA in the current study. This might have led to an underestimation of the severity of OA, and should be used for the standing fixed flexion view[30]. MRI was conducted without taking the recent loading or unloading conditions of the patients into consideration. Therefore, we cannot exclude the possibility that some mechanical stress recently experienced by the patients prior to undergoing these examinations may have affected the T2 values of the articular cartilage. The current study did not use any other MRI techniques, such as delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) or T1rho, which are also useful diagnostic modalities for

investigating any the changes in the extracellular matrix of the articular cartilage during OA progression.

In conclusion, the early stage OA-induced degenerative and morphological changes between the femoral- and the confronting tibial- or patellar- sides within the knee join were not the same. Namely, the degradation and destruction of the femoral articular cartilage showed a greater degree of deterioration than those of the tibial- and patellar- articular cartilage in the patients with early stage knee OA.

Contributions

SH, RS, MI and HK conceived and designed the study. SH, RS, MI, HK, LL, IF, MK, AY, YS, YT, HI and KK collected and registered patients data. SH, RS, MI, HK, LL, SH, IF, MK and AY had the major role in analysis and interpretation of the data, and contributed to drafting the report. KK also supervised the statistical analysis. All authors have read and approved the final manuscript.

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Conflict of interests

All authors declare that they have no competing interests.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2014.07.021.

References

1. Felson DT. Clinical practice. Osteoarthritis of the knee. N Engl J Med 2006;354:841–8.
2. Goldring MB, Goldring SR. Osteoarthritis. J Cell Physiol 2007;213:626–34.
3. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. Lancet 2005;365:965–73.
4. Ishijima M, Nakamura T, Shimizu K, Hayashi K, Kikuchi H, Soen S, *et al*. Intra-articular hyaluronic acid injection versus oral non-steroidal anti-inflammatory drug for the treatment of knee osteoarthritis: a multi-center, randomized, open-label, non-inferiority trial. Arthritis Res Ther 2014;16:R18.
5. Abramson SB, Attur M. Developments in the scientific understanding of osteoarthritis. Arthritis Res Ther 2009;11:227.
6. Liu L, Ishijima M, Futami I, Kaneko H, Kubota M, Kawasaki T, *et al*. Correlation between synovitis detected on enhanced-magnetic resonance imaging and a histological analysis with a patient-oriented outcome measure for Japanese patients with end-stage knee osteoarthritis receiving joint replacement surgery. Clin Rheumatol 2010;29:1185–90.
7. Ishijima M, Watari T, Naito K, Kaneko H, Futami I, Yoshimura-Ishida K, *et al*. Relationships between biomarkers of cartilage, bone, synovial metabolism and knee pain provide insights into the origins of pain in early knee osteoarthritis. Arthritis Res Ther 2011;13:R22.
8. Hunter DJ, Guermazi A, Roemer F, Zhang Y, Neogi T. Structural correlates of pain in joints with osteoarthritis. Osteoarthritis Cartilage 2013;21:1170–8.
9. Felson DT, Niu J, Guermazi A, Roemer F, Aliabadi P, Clancy M, *et al*. Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. Arthritis Rheum 2007;56:2986–92.
10. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, *et al*. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039–49.
11. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
12. Ravaud P, Giraudeau B, Auleley GR, Chastang C, Poiraudeau S, Ayral X, *et al*. Radiographic assessment of knee osteoarthritis: reproducibility and sensitivity to change. J Rheumatol 1996;23:1756–64.
13. Sharma L, Chmiel JS, Almagor O, Felson D, Guermazi A, Roemer F, *et al*. The role of varus and valgus alignment in the initial development of knee cartilage damage by MRI: the MOST study. Ann Rheum Dis 2013;72:235–40.
14. Buckland-Wright JC, Macfarlane DG, Williams SA, Ward RJ. Accuracy and precision of joint space width measurements in standard and macroradiographs of osteoarthritic knees. Ann Rheum Dis 1995;54:872–80.
15. Shimura Y, Kurosawa H, Sugawara Y, Tsuchiya M, Sawa M, Kaneko H, *et al*. The factors associated with pain severity in patients with knee osteoarthritis vary according to the radiographic disease severity: a cross-sectional study. Osteoarthritis Cartilage 2013;21:1179–84.
16. Liu L, Ishijima M, Kaneko H, Futami I, Sadatsuki R, Hada S, *et al*. Disability for daily living is a predictor for joint replacement in patients with end-stage knee osteoarthritis. J Bone Miner Metab 2014;32:192–9.
17. Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, *et al*. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage 2004;12:177–90.
18. Joseph GB, Baum T, Carballido-Gamio J, Nardo L, Virayavanich W, Alizai H, *et al*. Texture analysis of cartilage T2 maps: individuals with risk factors for OA have higher and more heterogeneous knee cartilage MR T2 compared to normal controls–data from the osteoarthritis initiative. Arthritis Res Ther 2011;13:R153.
19. Gold GE, Burstein D, Dardzinski B, Lang P, Boada F, Mosher T. MRI of articular cartilage in OA: novel pulse sequences and compositional/functional markers. Osteoarthritis Cartilage 2006;14(Suppl A):A76–86.
20. Lyyra T, Kiviranta I, Vaatainen U, Helminen HJ, Jurvelin JS. In vivo characterization of indentation stiffness of articular cartilage in the normal human knee. J Biomed Mater Res 1999;48:482–7.
21. Joseph GB, Baum T, Alizai H, Carballido-Gamio J, Nardo L, Virayavanich W, *et al*. Baseline mean and heterogeneity of MR cartilage T2 are associated with morphologic degeneration of cartilage, meniscus, and bone marrow over 3 years–data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2012;20:727–35.
22. Peh WC, Chan JH. The magic angle phenomenon in tendons: effect of varying the MR echo time. Br J Radiol 1998;71:31–6.

23. Yoshioka H, Schlechtweg PM, Kose K. Magnetic Resonance Imaging. Elsevier; 200934–48.
24. Wirth W, Hellio Le Graverand MP, Wyman BT, Maschek S, Hudelmaier M, Hitzl W, *et al*. Regional analysis of femorotibial cartilage loss in a subsample from the Osteoarthritis Initiative progression subcohort. Osteoarthritis Cartilage 2009;17:291–7.
25. Smith HE, Mosher TJ, Dardzinski BJ, Collins BG, Collins CM, Yang QX, *et al*. Spatial variation in cartilage T2 of the knee. J Magn Reson Imaging 2001;14:50–5.
26. Widmyer MR, Utturkar GM, Leddy HA, Coleman JL, Spritzer CE, Moorman 3rd CT, *et al*. High body mass index is associated with increased diurnal strains in the articular cartilage of the knee. Arthritis Rheum 2013;65:2615–22.
27. Eckstein F, Hudelmaier M, Putz R. The effects of exercise on human articular cartilage. J Anat 2006;208:491–512.
28. Wong BL, Sah RL. Mechanical asymmetry during articulation of tibial and femoral cartilages: local and overall compressive and shear deformation and properties. J Biomech 2010;43:1689–95.
29. Mosher TJ, Liu Y, Yang QX, Yao J, Smith R, Dardzinski BJ, *et al*. Age dependency of cartilage magnetic resonance imaging T2 relaxation times in asymptomatic women. Arthritis Rheum 2004;50:2820–8.
30. Niinimaki T, Ojala R, Niinimaki J, Leppilahti J. The standing fixed flexion view detects narrowing of the joint space better than the standing extended view in patients with moderate osteoarthritis of the knee. Acta Orthop 2010;81:344–6.