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The medial compartment and patellofemoral joint degenerate more severely in early stage knee osteoarthritis: a cross-sectional study

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Abstract. – OBJECTIVE: The purpose of this study was to compare the differences of degenerative characteristics of medial, lateral regions, femoral, patellar, and tibia parts of the knee joint in the early-stage of knee osteoarthritis (OA).

PATIENTS AND METHODS: A total of 66 patients with early stage knee OA and 22 healthy volunteers who have no knee-related clinical symptoms were enrolled in this cross-sectional study. T2 mapping and 3D dual-echo images were acquired with a 3.0T MR scanner. The degenerative changes of the articular cartilage were quantified by a T2 mapping and cartilage thicknesses analysis. Any structural changes were conducted using the Whole Organ Magnetic Resonance Imaging Score (WORMS).

RESULTS: In patients with knee OA, the thicknesses of medial cartilages were significantly thinner than lateral ones (2.13 mm *vs*. 2.34 mm, $p<0.0001$), but with higher T2 values (40.38 ms *vs*. 38.4 ms, $p<0.0001$) and WORMS scores (12.12 vs. 0.47, $p=0.004$). No significant differences were observed between medial and lateral cartilage in the healthy volunteers. The T2 values of the femoral ($p<0.001$) and patellar ($p=0.012$) cartilages of OA patients were higher than that of the healthy controls. Within OA group, the T2 values of femoral ($p<0.0001$) and patellar ($p<0.0001$) cartilages were higher than tibial ones. Moreover, the WORMS scores of femoral ($p=0.001$) and patellar ($p<0.0001$) cartilages were higher than that of the tibial ones.

CONCLUSIONS: This study demonstrates that the medial compartment and patellofemoral knee joint degenerate more severely in patients with early-stage knee OA.

Key Words:
Knee osteoarthritis, Magnetic resonance imaging (MRI); Cartilage thickness, T2 mapping, Whole Organ Magnetic Resonance Imaging Score (WORMS).

Introduction

Knee osteoarthritis (OA) is a widespread degenerative joint disease for the elderly, which manifests articular cartilage-based total knee degeneration. Loss of hyaline cartilage is one of the important signs of OA degeneration, while subchondral bone, meniscus, and synovium can also be involved in the progression of OA. At present, how knee OA progresses remains unclear. For example, it is uncertain whether the medial and lateral degenerations of the knee synchronize, or whether degeneration degrees of femur, tibia, and patellar are the same. In the clinic, patients often present with different stages of disease progression. If clinicians can define the typical characteristics of early knee OA by determining disease stage in patients with clinical symptoms, radiology, and laboratory examinations, it will remarkably benefit early prevention and stage-specific treatments. Fortunately, with the rapid development of MRI technology, articular cartilage morphology, i.e., thickness and volume, changes in physiological components can be quantitatively assessed using emerging techniques[1,2].

Quantitative T2 mapping can measure cartilage degeneration by fathoming water content of cartilage and change of collagen fibers. Additionally, Whole Organ Magnetic Resonance Imaging Score (WORMS) covers characteristics of knee joint lesions comprehensively, evaluating the changes of cartilage, bone marrow edema of subchondral bone, bone cysts, osteophytes, meniscus, synovium, and ligaments[3]. These MRI techniques and evaluation methods help us understand the early stages of knee OA more clearly.

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The aim of this study was to determine MRI features of early degeneration stages of knee OA and compare the differences of degenerative characteristics of medial, lateral regions, femoral, patellar, and tibia parts of the knee joint.

Patients and Methods

Participants

This is a level 2 cross-sectional study that was approved by the Ethics Committee and registered in the national Clinical Trial Registry. 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 had knee OA and underwent the initial medical examination at our outpatient clinic between May 2015 and December 2015. In this cross-sectional study, all enrolled subjects were assigned to the knee OA and healthy control groups. All participants signed informed consent.

Diagnosis of symptomatic knee OA was made according to the American College of Rheumatology (ACR) 1986 criteria[4]. To be included in the study, patients must have met the following criteria: (1) age between 40 and 75 years old; (2) repeated knee pain, morning stiffness, and joint movement disorders; (3) Kellgren-Lawrence (KL) score $\leq$ 2. The exclusion criteria were as follows: (1) the presence of cardiovascular, liver, kidney, hematopoietic system or other serious primary diseases; (2) rheumatoid arthritis, gouty arthritis or other arthritic diseases, other diseases affecting the function of lower limb; (3) intramuscular injection, joint injection, soft tissue injection or oral medication of steroid, or oral medication of NSAIDs or cartilage protective agents (glucosamine sulfate or chondroitin sulfate) within 1 month prior; (4) any contraindication to MRI scanning. Healthy volunteers without MRI-based OA changes were recruited, and the T2 values were also evaluated to avoid the effect of the magic angle effect (MAE). Healthy young people must have met the following criteria: (1) age between 20 and 35 years old; (2) without any symptoms of arthritis; (3) no symptoms of arthritis, pain, stiffness, swelling, movement disorders of knee joint, trauma, history of deformities, surgery, arthritic diseases, oral medication of NSAIDs, or joint injection, soft tissue injection of steroid, contraindication to MRI scanning.

MRI Equipment and Protocols

All MRI scans were performed using a 3-T MRI scanner (MAGNETOM Verio, Siemens, München, Germany) with a dedicated eight-channel knee coil. Typical acquisition parameters of 3D dual-echo in steady-state were as follows: field of view (FOV), 140 × 140 mm; repetition time (TR), 16.3 ms, Echo Time (TE), 4.7 ms; matrix, 336 × 448 with a total scan time of 3 min and 27 s. Typical acquisition parameters of T2 mapping were as follows: seven multi-echo, spin-echo sequence, TR, 2700 ms, TE, 10.3/20.6/30.9/41.2/51.5/61.8/72.1 ms; FOV, 180 × 180 mm; matrix, 384 × 484 with a total scan time of 10 min and 12 s. All subjects were allowed to rest for at least 30 minutes to minimize the load of the knee.

Measurement of the Thickness of Articular Cartilage

The thickness of articular cartilage was measured in 3D DESS imaging. Knee articular cartilage is an irregular body composed of a curved surface. To truly reflect the thickness of articular cartilage, a thickness which presented the length from the cartilage surface to the 'tide line' was measured in the sagittal plane, coronal plane, and cross-section, respectively, and a mean value was calculated by three layers which were the thickest level and other two adjacent layers.

Sagittal plane: the middle layer of patellar cartilage, which fully exposed meniscus and cartilage, was the thickest of and was measured, and patellar cartilage was divided into four parts, measuring the cartilage thickness of 1/4, 1/2, 3/4. The femoral cartilage thickness of the joint between the femoral cartilage and the lines which were drawn with the line linked the anterior and posterior margin of the femoral epiphyseal line at 45°, 90°, and 135°, respectively, was measured. Meanwhile, tibial cartilage thickness of the joint between the first 1/4, middle 1/2, last 1/4 of the tibial plateau was measured (Figure 1A-B).

Coronal plane: the middle layer thickness of the thickest cartilage of femur medial condyle, femur lateral condyle, tibial medial plateau, and tibial lateral plateau were measured; moreover, also the thickness of the joint between the cartilage and vertical line, which was made from the line of 1/4, 1/2, 3/4 respectively linked the edges of two sides of each plateau to the cartilage surface, was measured (Figure 1C).

Cross-section: the thickness of the patella cartilage was measured, and the thickness of the joint between the cartilage and vertical line, which was

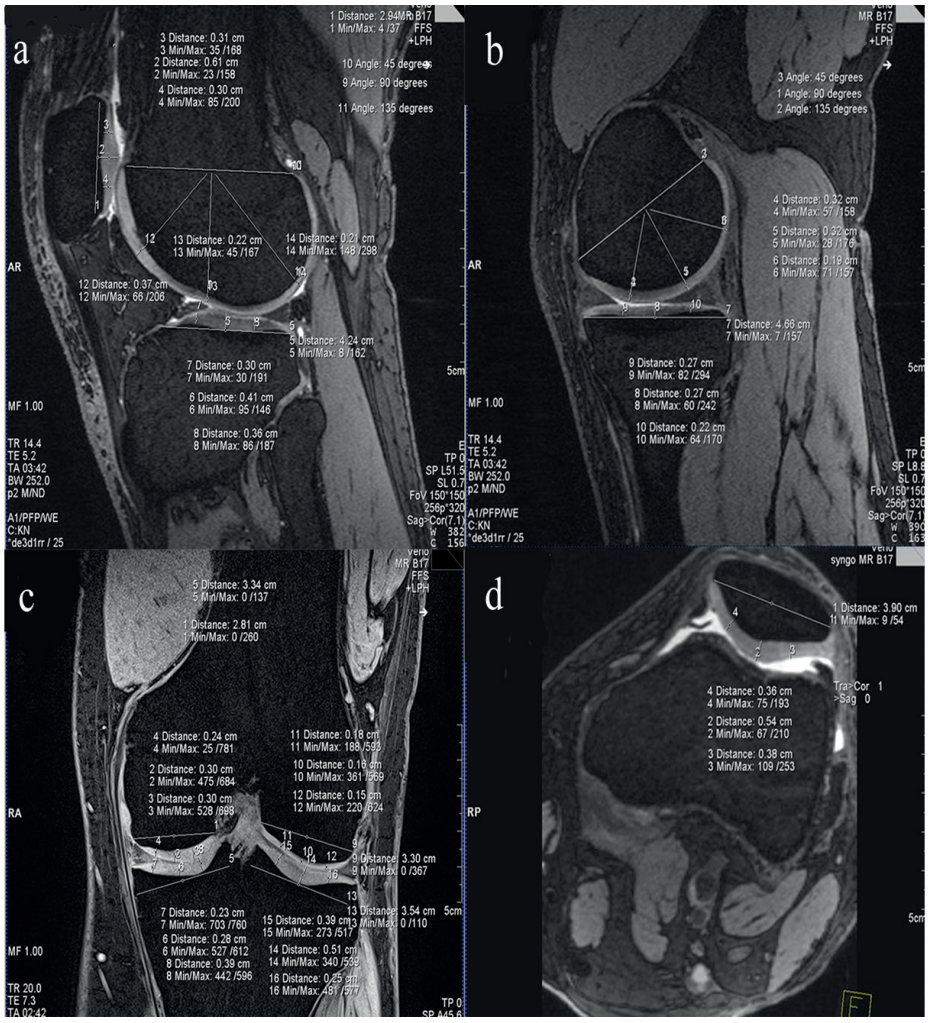

Figure 1. A, A sagittal section shows the cartilage thickness of lateral femur, lateral tibia and patellar. **B,** A sagittal section shows the cartilage thickness of media femur and medial tibia from. **C,** A coronal section shows the cartilage thickness of femur and tibia. **D,** A representative axial cut of a knee MR image shows the cartilage thickness of patellar.

made from the line of 1/4, 1/2, 3/4 respectively, linked the edges of patella two sides to the cartilage surface, was measured (Figure 1D).

WORMS

The femoral condyle, tibial plateau and patella were divided into medial area (M) and lateral area (L) by WORMS; each side of the femoral condyle and tibial plateau were divided into the anterior area (A), middle area (C) and posterior area (P) by meniscus, accordingly the knee joint which was divided into 14 assessment sections (Figure 2). The cartilage, bone marrow edema, bone cyst, bone wear and osteophyte of 14 assessment sections were evaluated on 3D-DESS sequence images, as well as damage of ligament and meniscus.

The Division of Interested Region of Articular Cartilage and the Measurement of T2 Value

The division of the interested region of articular cartilage was referenced to the WORMS division, and T2 values of cartilage of 14 assessment sections were evaluated. Pseudo-color maps of T2 values were generated automatically by Siemens system, where T2 values of the interested region were measured according to the division of cartilage sub-region, excluding the artifacts, effusion, and area of which T2 values were more than 200 ms. All radiographs were quantified independently by two readers (a) who were blinded to the patients' baseline characteristics.

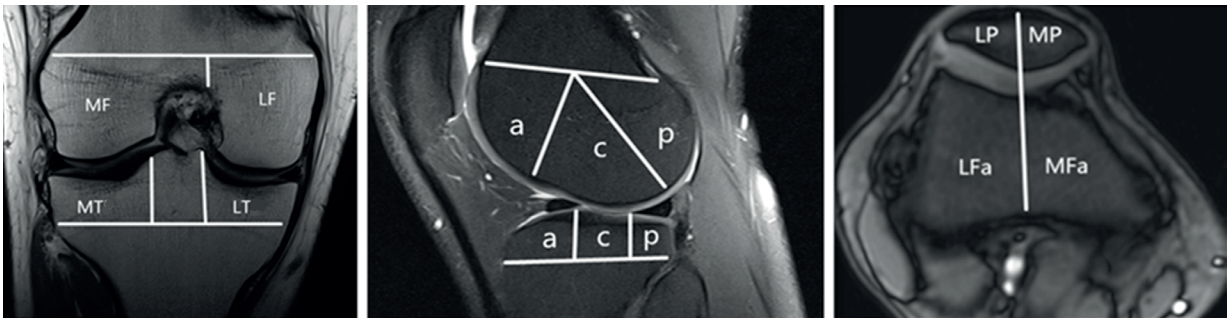

Figure 2. The division of cartilage for WORMS values. Femoral condyle, tibial plateau and patella are divided into medial (**M**) and lateral (**L**). Each side of the femoral condyle, tibia plateau to meniscus as the boundary is divided into the anterior area (**A**), central area (**C**) and posterior area (**P**). MF: medial femur; LF: lateral femur; MT: medial tibia; LT: lateral tibia; LP: lateral patella; MP: medial patella; LFa: lateral femoral anterior region; MFa: medial femoral anterior region.

Statistical Analysis

Statistical analyses were made using the software programs PASW statistics 17.0 (SPSS Inc., Chicago, IL, USA). A two-sided test was used, and significance level was set at a p-value < 0.05. Paired sample t-tests were used to detect significant differences in OA patients and healthy young people between cartilage thickness and cartilage T2 value of each knee joint partition. Independent-samples t-tests were used to value significant differences in cartilage thickness and cartilage T2 value of different partition of knee joint between two groups. WORMS assessment of different parts of OA patients was analyzed using nonparametric tests of two paired samples.

Results

Subject Characteristics

Twenty-two healthy adults (mean age of 26 years) and 66 knee OA patients (mean age of 59 years) participated in the study (from May 2015 to December 2015). In the OA group, 41.8% of the patients were KL grade 1 and the rest were KL grade 2. No significant differences in body weight and BMI were observed between the two groups (Table I).

Comparison of the Degenerations Between Medial and Lateral Knee Joint

The thicknesses of knee joint cartilages varied between medial and lateral. The thickness of medial cartilage (F=3.53, p=0.001), and lateral cartilage (F=3.89, p<0.0001) in OA group was lower than that of the healthy group (Table II). Lateral cartilages were thicker than medial cartilage in both healthy group (F=6.73, p<0.0001) and OA group (F=6.27, p<0.0001). The T2 values of medial cartilage (F=2.13, p =0.003) in OA group were higher than that of the healthy group (Table II). In healthy group, no difference of T2 values was observed between medial and lateral cartilage as well as medial and lateral meniscus. While, in OA group, the T2 values of medial cartilage (t=4.171, p<0.0001) and medial meniscus (t=2.35, p=0.022) were higher than that of lateral cartilage (Table II). WORMS scores of different

Table I. Comparison of baseline data between healthy and OA groups.

	Healthy group	OA group	F	p
n	22	66	–	–
Ages	26.09 (2.89)	58.8 (7.69)	14.17	< 0.0001
Height (m)	1.71 (0.086)	1.60 (0.08)	0.02	< 0.0001
Weight (kg)	67.48 (12.98)	62.07 (11.71)	1.133	0.071
BMI (kg/m2)	22.77 (2.61)	24.17 (3.33)	0.863	0.075
KL-0	22 (100%)	4 (5.97%)	–	–
KL-1	0	24 (35.8%)	–	–
KL-2	0	39 (58.2%)	–	–

Note the data are the means (SD).

Table II. Comparison of thickness and T2 values of cartilage between healthy and OA groups.

	Project	Healthy group	OA group	F	p
Medial	Thickness (mm)	2.39 (0.31)*	2.13 (0.29)*	3.53	0.001
	T2 values (ms)	37.57 (3.04)	40.38 (3.85)*	2.128	0.003
Lateral	Thickness (mm)	2.74 (0.42)	2.34 (0.40)	3.89	< 0.0001
	T2 values (ms)	36.7 (3.29)	38.4 (3.59)	0.248	0.044
Patella	Thickness (mm)	3.54 (0.63)**	2.49 (0.75)**	5.93	< 0.0001
	T2 values (ms)	39.06 (4.79)	43.01 (6.63)	1.056	0.012
Femur	Thickness (mm)	2.00 (0.25)#	1.94 (0.25)#	0.97	0.337
	T2 values (ms)	39.54 (3.02)#	42.61 (3.58)#	1.274	0.001
Tibia	thickness (mm)	2.70 (0.40)##	2.43 (0.42)	2.56	0.012
	T2 values (ms)	32.82 (2.87)##	32.66 (3.42)##	1.153	0.853

Note data indicates mean (SD). *Indicates significant difference (p<0.0001) between the medial and lateral cartilage. **Indicates significant difference (p<0.0001) between the patella and femur cartilage, #indicates significant difference (p<0.0001) between the femur and tibia cartilage. #Indicates significant difference (p<0.0001) between the tibia and patella cartilage.

parts varied in OA group. WORMS scores of medial cartilages were higher than that of lateral cartilages (Z=2.867, p=0.004); meanwhile, the cartilage injury and bone marrow edema in medial cartilage were more evident (Table III).

Comparison of the Degenerations Between the Femur, Tibia and Patellar

The thickness of patella (F=5.93, p<0.0001) and tibial articular cartilage (F=2.56, p=0.012) in OA group was lower than that of the healthy group. There were no significant differences in thickness of femoral articular cartilage between the two groups (Table II). The thickest and thinnest cartilages were patellar cartilage (3.54±0.63 mm) and femoral cartilage (2.70±0.40 mm) in healthy group, while the patellar cartilage was thicker than that of tibia. In OA group, patellar cartilage (2.49±0.75 mm) was the thickest and femoral cartilage (1.94±0.25 mm) the thinnest, whereas the thickness of patellar cartilage was equal to that of tibia cartilage (Table II). The T2 values of femur cartilage (F=1.27, p<0.001) and patella cartilage (F=1.06, p=0.012) in OA group were higher than that of the healthy group (Table II, Figure 3A-B). In healthy group, the T2 value of femur cartilage was higher than that of patella cartilage, and both were higher than that of tibia cartilage (p<0.0001). In OA group, the T2 values of femur cartilage (42.61±3.58 ms) and patella cartilage (43.01±6.63 ms) were higher than that of tibia cartilage (32.66±3.42 ms) while T2 value of patella cartilage was slightly higher than that of femur cartilage (Table II). WORMS scores of different parts varied in OA group. With higher WORMS scores, degrees of cartilage injury, bone marrow edema and osteophytes in patella and femur cartilage were higher than that of the tibia

Table III. Comparison of WORMS scores in different parts of OA group.

	Z	p
Medial WORMS-lateral WORMS	2.867	0.004
Medial cartilage-lateral cartilage	2.465	0.014
Medial BML-lateral BML	2.481	0.013
Medial cyst-lateral cyst	3.69	0.712
Medial osteophyte-lateral osteophyte	1.285	0.199
Medial meniscus-lateral meniscus	1.088	0.277
Femur WORMS-tibia WORMS	3.355	0.001
Patella WORMS-tibia WORMS	2.809	0.005
Femur cartilage-tiba cartilage	6.343	< 0.0001
Patella cartilage-tibia cartilage	5.389	< 0.0001
Femur BML-tiba BML	3.71	< 0.0001
Patella BML-tibia BML	4.959	< 0.0001
Femur osteophyte-tibia osteophyte	3.404	0.001
Patella osteophyte-tibia osteophyte	4.274	< 0.0001

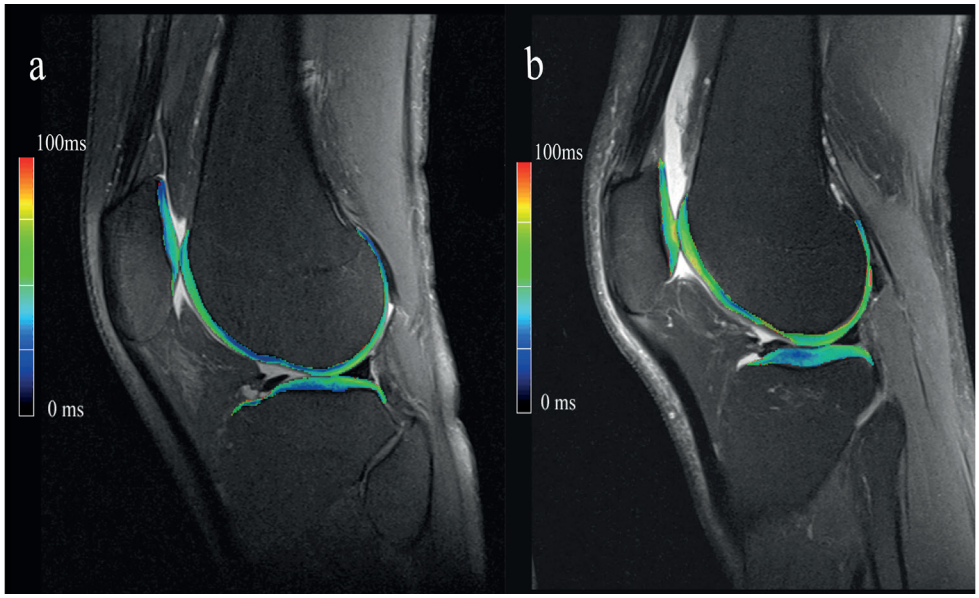

Figure 3. A, The color of T2 mapping shows uniform in health. **B,** The T2 values of femur cartilage and patella cartilage in OA shows higher than that of the healthy people.

cartilages (Table III). Cartilage injury and bone marrow edema occurred mainly at patellofemoral joint surface, accounting for 76.34% and 69.38%, respectively.

The MRI Features of Early Degeneration Stages of Knee OA

Knee OA is usually accompanied by varying degrees of cartilage injury and osteophytes, and with a high incidence rate (86.4%) of bone marrow edema. A significant association was found between bone marrow edema and cartilage injury (R=0.643, p<0.0001). Approximately 45% OA patients suffered from popliteal cysts.

Discussion

Our study indicated that, based on MRI imaging, knee OA patients in early stages presented not only degeneration of cartilage (increased cartilage T2 values and decreased cartilage thickness), but also various changes of meniscus which occurred around cartilage and subchondral bone manifesting meniscus injury, bone marrow edema of subchondral bone, osteophyte, and popliteal cyst. The degeneration of knee joints differed in different parts; for instance, patella cartilage and femur cartilage were worse than tibia cartilage, and injury of medial cartilage was more obvious than lateral cartilage.

Young adults with traumatic injury to the knee joint are at substantially increased risk for osteoarthritis at the same joint later in life[5]. In addition, an increased risk of developing knee OA was associated with participation in soccer, ice hockey, and tennis, but not running[6]. Magnetic resonance quantitative and semi-quantitative evaluation techniques are also beneficial for assessing early knee injury in athletes and guiding clinical interventions.

Differences in the Medial and Lateral Knee Regions of OA Patients

No T2 value difference was observed between medial and lateral cartilages in healthy group, while T2 value of medial cartilage was significantly higher than that of lateral cartilage in OA group. The thickness of medial cartilage was less than that of lateral side, while WORMS of medial cartilage is higher than that of lateral cartilage in OA group. All these results demonstrated that the medial region, especially medial cartilage, was much easier to be damaged when knee OA occurred. Imbalance of cartilage thickness could make the knee vulnerable for OA in medial region. By 3T MR using a 2D multi-echo spin echo (MESE) sequence for T2 mapping, Friedrich et al[7] observed that T2 values of cartilage in the medial compartment were significantly higher (p=0.0043) than those in the lateral compartment, and patients with varus alignment had signifi-

cantly higher T2 values of cartilage than patients with valgus alignment. A report from European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)[8] presented that medial compartment cartilage volume/thickness loss seemed to predict progression to total knee replacement (TKR). In addition, an OAI-based analysis suggested cartilage thickness loss in the central and total medial femorotibial compartment increased probability of TKR[9].

The thickness of cartilage would become thinner when knee OA occurs. Not only the medial cartilage and meniscus are damaged, but also subchondral bone goes through a series of changes, and among them, medial bone marrow edema is the most evident. Medial bone marrow edema can also predict the occurrence of TKR. Raynauld et al[10] analyzed the results from a 6-year study. Multivariate analysis showed that baseline severe medial meniscal tear (p=0.023) and presence of medial BML (p=0.025) were the strongest, independent long-term predictors of TKR. From a one-year follow-up study in knee OA patients, Tanamas et al[11] found that the medial bone marrow edema was strongly associated with loss of medial cartilage and predicted TKR 4 years later. Therefore, finding a novel treatment that can slow the deterioration of medial cartilage and bone marrow edema will be of great benefit to reduce the demand of TKR or delay TKR.

Differences of Knee Degeneration in the Femur, Patella, and Tibia

The thicknesses of the femur, patella and tibia cartilages are significantly different. The thicknesses of femoral cartilages in healthy and OA groups were the thinnest, while the most significant difference between healthy control and OA groups was observed for the patellar cartilages. An autopsy study[12] found that the average thickness of femoral cartilage was 2.5 mm and the average thickness of patellar cartilage was 4.5 mm. Thinner femoral cartilage was more susceptible to damage in daily flexion. In addition, the T2 values of femoral and patellar cartilages were both significantly higher than the tibial cartilage in OA group. A recent MRI study[13] found that the T2 values of femoral condyle and groove in patients with early stage knee OA were significantly increased in comparison to those of the healthy controls, and the WORMS cartilage and osteophyte scores of the femoral articular cartilage were significantly higher than those in the patellar-articular and tibial-articular cartilage in the patients with early stage knee OA. This study suggested that the femoral articular cartilage's degradation and destruction resulted from greater degrees of deterioration than those of the tibial-articular and patellar-articular cartilage. Wirth et al[14] measured thickness of articular cartilage of femur and tibia by 3T MR, and found the rate of cartilage loss of femoral medial compartment tended to be greater for tibial medial compartment in OA patients with K/L grade 2 and 3. Degeneration of femur, patellar cartilage, and bone marrow edema, bone cyst, osteophyte degeneration of these two parts were also significantly worse than those in tibia. As the medial patellofemoral joint withstands more stress by the flexion movement of knee, medial patellofemoral articular surface is much easier to degenerate.

MRI Features of Early Degeneration Stages of Knee OA

A large number of clinical studies[15,16] have confirmed that the loss of articular cartilage volume and thickness, and changes in cartilage components are sensitive indicators to predict knee OA progression. A reasonable selection of MRI scan sequences and parameters is a prerequisite for obtaining high SNR images and highlighting the subjects. A double echo steady state sequence (DESS) was used in our study, which can improve the cartilage resolution and clearly distinguish between cartilage and synovial fluid. 3D-DESS sequence can be applied to conduct more accurate analysis of knee cartilage morphology[17] with a clear display of cartilages and advantages in the measurement of volume and thickness of cartilage[18]. This sequence has shown higher sensitivity in a longitudinal study of changes in the articular cartilage thickness[19]. Our study measured the thickness of cartilage from different parts (patellar, femur and tibia) and dimensions (transverse, coronal and sagittal planes) using 3D-DESS sequence imaging. The thickness of cartilage in OA patients was lower than that in healthy people, and significant difference was observed in the thickness of patellar cartilage.

T2 values are sensitive monitors of the changes in water content of cartilage matrix and collagen fibers and have a high replicating rate in a multi-center clinical trials[20]. No matter what angle to observe cartilage, e.g., tangent, transition, radiation or calcification, the accuracy of the T2 value remains satisfactory[21], and this is why T2-mapping is widely used in the study of knee

OA[22]. Although T2 value is sensitive in articular cartilage of intact morphology in early-stage degeneration, it is difficult to assess damaged cartilage of advanced knee OA patients[23]. In this study, the OA patients had less than 2 in KL degree. T2 value of patellar cartilage and femoral cartilage in OA group was approximate 3 ms and 2 ms more than that in healthy people, respectively. While there were no significant differences in T2 value of tibia cartilage between the two groups. Increased T2 value of lesion may be one of early manifestations of OA.

At present, the staging of knee OA has not been clearly defined, and usually KL $\leq$ 2 score is used as the criteria of early and mid-stage OA, but its poor repeatability and sensitivity limit its use in accurate disease staging[24]. Magnetic resonance better detects cartilage changes than X-ray. Luyten et al[25] recently defined criteria of early knee OA by MRI semi-quantitative scoring system, which more comprehensively reflects the status of early knee OA. They only described MRI of cartilage, meniscus and bone marrow edema for early knee OA, which still do not fully reflect the actual status of early OA. Additionally, the use of two parallel semi-quantitative scoring systems generates hardship for the clinical practice. Identification of stages of knee OA by T2 value of cartilage and total WORMS will significantly contribute to early diagnosis, treatment, evaluation of intervention of knee OA. Of course, such protocol needs to be supported by large sample pool from multi-center clinical trials.

Despite the promising results, some limitations of our study should be taken into account. The number of subjects was not large enough. To find the features of early stage knee OA, future studies with more patients are needed. The current study did not use histological or immunohistochemical analysis, which are also useful diagnostic modalities for investigating any changes of the articulation during OA progression.

Conclusions

In brief, the medial compartment knee joint degenerated more severely than lateral ones in patients with early stage knee OA. The femoral and patellar-articular cartilage's degradation and destruction showed a greater degree of deterioration than those of the tibial-articular cartilage. Moreover, OA patients not only manifest decreased thickness of articular cartilage and increased T2 values of cartilage, but also present bone marrow edema of articular cartilage, bone cysts, meniscus injury, popliteal cysts, etc.; therefore, knee OA is a total knee degeneration characterized by articular cartilage degeneration.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

Yongfang Zhao contributed to the conception, protocol development, and design of the study. Guangyue Yang and Hailing Guo participated in data acquisition, analysis, and interpretation. Tao Li, Haibin Shang and Yinyu Shi contributed to data acquisition, and data interpretation. All authors have contributed significantly to the various stages in this manuscript's writing and approved the final version of the paper. The authors would like to thank Mr Songhua Zhan and his colleagues in Shuguang Hospital (Shanghai, China) for their help with the MRI analysis.

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