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WJO covers topics concerning arthroscopy, evidence-based medicine, epidemiology, nursing, sports medicine, therapy of bone and spinal diseases, bone trauma, osteoarthropathy, bone tumors and osteoporosis, minimally invasive therapy, diagnostic imaging. Priority publication will be given to articles concerning diagnosis and treatment of orthopedic diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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ORIGINAL ARTICLE

Observational Study

T1ρ/T2 mapping and histopathology of degenerative cartilage in advanced knee osteoarthritis

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Author contributions: All authors participated in the interpretation of data, revision and final approval of the manuscript; Kester BS interpreted the data, drafted and completed the manuscript; Carpenter PM additionally carried out the histologic analysis; Yu HJ, Nozaki T, Kaneko Y and Yoshioka H equally participated in the study design, radiographic interpretation, and statistical analysis; Yoshioka H and Schwarzkopf R were the principle investigators, lead of study conception and guided manuscript completion.

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Abstract

AIM

To investigate whether normal thickness cartilage in osteoarthritic knees demonstrate depletion of proteoglycan or collagen content compared to healthy knees.

METHODS

Magnetic resonance (MR) images were acquired from 5 subjects scheduled for total knee arthroplasty (TKA) (mean age 70 years) and 20 young healthy control subjects without knee pain (mean age 28.9 years). MR images of T1ρ mapping, T2 mapping, and fat suppressed proton-density weighted sequences were obtained.

Following TKA each condyle was divided into 4 parts (distal medial, posterior medial, distal lateral, posterior lateral) for cartilage analysis. Twenty specimens (bone and cartilage blocks) were examined. For each joint, the degree and extent of cartilage destruction was determined using the Osteoarthritis Research Society International cartilage histopathology assessment system. In magnetic resonance imaging (MRI) analysis, 2 readers performed cartilage segmentation for T1ρ/T2 values and cartilage thickness measurement.

RESULTS

Eleven areas in MRI including normal or near normal cartilage thickness were selected. The corresponding histopathological sections demonstrated mild to moderate osteoarthritis (OA). There was no significant difference in cartilage thickness in MRI between control and advanced OA samples [medial distal condyle, P = 0.461; medial posterior condyle (MPC), P = 0.352; lateral distal condyle, P = 0.654; lateral posterior condyle, P = 0.550], suggesting arthritic specimens were morphologically similar to normal or early staged degenerative cartilage. Cartilage T2 and T1ρ values from the MPC were significantly higher among the patients with advanced OA (P = 0.043). For remaining condylar samples there was no statistical difference in T2 and T1ρ values between cases and controls but there was a trend towards higher values in advanced OA patients.

CONCLUSION

Though cartilage is morphologically normal or near normal, degenerative changes exist in advanced OA patients. These changes can be detected with T2 and T1ρ MRI techniques.

Key words: T1rho; Osteoarthritis; Magnetic resonance imaging; Cartilage; Knee

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Core tip: Magnetic resonance images of eleven healthy knees and five knees with advanced osteoarthritis (OA) were studied using T1ρ and T2 mapping. Histopathologic samples were also taken from the five osteoarthritic knees following total knee arthroplasty. Our results indicate that even though cartilage is morphologically normal or near normal, cartilage degenerative changes exist in advanced OA patients. This suggests that normal thickness cartilage or mild cartilage thinning in the advanced OA knee demonstrates depletion of proteoglycan or collagen content compared with similar appearing cartilage in young healthy knees. These early changes can be detected with T2 and T1ρ MRI techniques.

Kester BS, Carpenter PM, Yu HJ, Nozaki T, Kaneko Y, Yoshioka H, Schwarzkopf R. T1ρ/T2 mapping and histopathology of degenerative cartilage in advanced knee osteoarthritis. *World J Orthop* 2017; 8(4): 350-356 Available from: URL: http://www.wjgnet.com/2218-5836/full/v8/i4/350.htm DOI: http://dx.doi.org/10.5312/wjo.v8.i4.350

INTRODUCTION

Osteoarthritis (OA) is one of the fastest growing medical conditions worldwide, affecting at least 27 million people in the United States alone[1,2]. It is a major contributor to functional disability and loss of autonomy in older adults[3]. These factors represent a significant health and financial burden to the general population[2,4]. Knee and hip OA cause the greatest burden of disability, leading to the need for prosthetic joint replacements in the most severe cases[5]. Decreasing the need for such procedures, and costs to both the patient and society, motivates the need for research into disease prevention and early detection.

OA is characterized by the progressive loss of articular cartilage. However, significant damage to the collagen-proteoglycan matrix and elevation of cartilage water content are believed to precede the loss of cartilage and consequent symptoms of knee OA[6,7]. Magnetic resonance imaging (MRI) techniques are been developed over the past decade that allow for the detection of these early and subtle changes to the cartilage matrix[8-11]. Among these techniques, T1ρ has stood out as a high sensitivity option to detect early changes without the use of contrast agents[7].

Prior studies have already demonstrated increased cartilage T1ρ values, a surrogate of cartilage damage, in patients with knee OA[12-15]. Specifically, T1ρ and T2 values are known to be elevated in asymptomatic, healthy subjects with early stage OA compared to individuals without focal lesions[13]. While severe focal lesions are common indications for total knee replacement, patients may also be considered for joint sparing or cartilage preservation procedures. We aim to determine whether normal appearing cartilage by MRI in the non-symptomatic regions of advanced knee OA demonstrate depletion of proteoglycan and collagen content by T1ρ and T2 mapping and to correlate these measurements with degenerative changes of cartilage by histology. We hypothesize that normal thickness cartilage or mild cartilage thinning (early staged cartilage degeneration) in advanced knee OA will demonstrate depletion of proteoglycan or collagen content, compared with similar appearing cartilage in young healthy knees.

MATERIALS AND METHODS

Study population

Five advanced OA patients scheduled for total knee arthroplasty (TKA) were enrolled in this study. A board certified orthopaedic surgeon (RS) recruited them (Kellgren-Lawrence score of 3 or 4; mean age 70 years, range 62-90 years; 2 men and 3 women). Twenty knees from 20 healthy volunteers (mean age 28.9 years, range

19-38 years; 13 men and 7 women) without any history of knee symptoms or prior knee surgery were used as an imaging control group. The study protocol was approved by the institutional review board and all subjects provided written informed consent before any study-related procedures were performed.

MRI

All MR studies were performed on a 3.0-T unit (Achieva, Philips Healthcare, Netherland) utilizing an 8-channel knee receive-only radiofrequency coil. Three sagittal MR images were acquired including fat suppressed (FS) proton density-weighted imaging (PDWI) sequence, T2 mapping sequence, and T1ρ mapping sequence. All sagittal images were obtained without oblique angulation, parallel to the magnetic static field (B0). Parallel imaging was used on all imaging sequences utilizing Sensitivity Encoding for MRI. The acquisition parameters were as follows. FS PDWI: 2D turbo spin-echo; Repetition time (TR)/echo time (TE) = 4311/30 ms, number of excitation (NEX) = 2, and total acquisition time = 3 min 35 s. T2 mapping: 2D turbo spin-echo; TR/TE = 2700/13, 26, 39, 52, 65, 78, 91 ms, NEX = 1 and total acquisition time = 13 min 26 s. T1ρ: 3D FS PROSET (Principle of Selective Excitation Technique); TR/TE = 6.4/3.4 ms, flip angle = 10°, echo train length = 64, NEX = 1, spin-lock frequency = 575 Hertz, time of spin-lock (TSL), 20, 40, 60 and 80 ms, and acquisition time = 4 min 9 s × 4. All images were obtained with field of view = 140 × 140 mm, slice thickness/gap = 3/0 mm, image matrix = 512 × 512, number of slices = 31 and effective in-plane spatial resolution = 0.27 × 0.27 mm. Each femoral condyle was divided into 4 areas: The medial distal condyle (MDC), medial posterior condyle (MPC), lateral distal condyle (LDC), and lateral posterior condyle (LPC). Therefore, a total of 20 areas of MRI of the femoral condyle from 5 patients with advanced OA were reviewed.

TKA

TKA was conducted as scheduled on each operative candidate. Surgically resected condyles were recovered intraoperatively and divided into 4 parts (MDC, MPC, LDC, LPC). A total of 20 specimens (bone and cartilage blocks) were histopathologically examined.

Pathology

The MDP, MPC, LDC and LDP of the distal femur removed at surgery were fixed in 10% neutral buffered formalin for at least 72 h, decalcified using dilute hydrochloric acid (Rapid Bone Decalcifier, American Master Tech Inc., Lodi CA) for two days, and post fixed in formalin for at least 2 more days. Sagittal sections across the entire mid portion of each of the condyles underwent routine paraffin embedding and staining with hematoxylin and eosin. In this way, the same region was sampled for each of the specimens, and maximum extent of the lesion could be assessed in the mid sagittal plane of each of the condyles. Additional paraffin sections were stained with Masson's trichrome and Alcian blue. For each joint, the degree and extent of cartilage destruction was determined using the Osteoarthritis Research Society International cartilage histopathology assessment system[16] by a pathologist with experience in bone and soft tissue pathology. For this system, the degree of cartilage destruction (OA grade) and the extent of destruction (OA stage) are multiplied to determine the OA score. The surgical edges were not assessed to avoid possible over-interpretation of surgical artifacts.

Imaging analysis

Images were transferred in Digital Imaging and Communications in Medicine format to a personal computer (Windows 7), which was used to perform all post-processing and analyses. T2 and T1ρ analyses were performed using in-house developed and implemented software in MatLab (MathWorks, Natick, MA) (Figure 1). Manual cartilage extraction of the femoral condyle in healthy volunteers (n = 20) and advanced OA patients (n = 5) was performed on both T2 and T1ρ images by a board-certified orthopaedic surgeon with 14 years of experience and a board-certified radiologist with 13 years of experience, independently. Images with TE = 26 in T2 and TSL = 20 in T1ρ were chosen for segmentation due to high signal-to-noise ratio compared to the other images, based on prior studies[17,18]. T2 and T1ρ values were measured in a range of -10 to 20 degrees for the distal condyle and 70 to 100 degrees for the posterior condyle (Figure 2). The angle 0 is defined along B0. We calculated average T2 and T1ρ values of two observers at each femoral condyle, and average thickness of the cartilage as pixel numbers in the segmented area at each condyle.

Statistical analysis

Differences in T2/T1ρ values and thickness of the cartilage between normal cartilage and advanced degenerative cartilage do not conform to normal distributions. These differences were assessed using a nonparametric Mann-Whitney U test. Statistical review of the study was performed by a researcher with training in biomedical statistics. SPSS Statistics version 22 (IBM, Armonk, New York) was used for calculations. In all cases, a P value of 0.05 or less was deemed statistically significant.

RESULTS

A total of 20 areas on MRI of the femoral condyles from 5 advanced OA patients were reviewed. Eleven areas including normal or near normal cartilage thickness (2 MDCs, 2 MPCs, 4 LDCs, 3 LPCs) were selected. The average OA grade, stage, and, scores of corresponding specimens (bone blocks and cartilage) were 3.82 (range: 3-4.5), 3.45 (range: 2-4), and 13.1 (range: 7-16), respectively, compatible with mild to moderate OA (Table 1). Examples of FS PDWI, hematoxylin and eosin stain, Alcian blue stain,

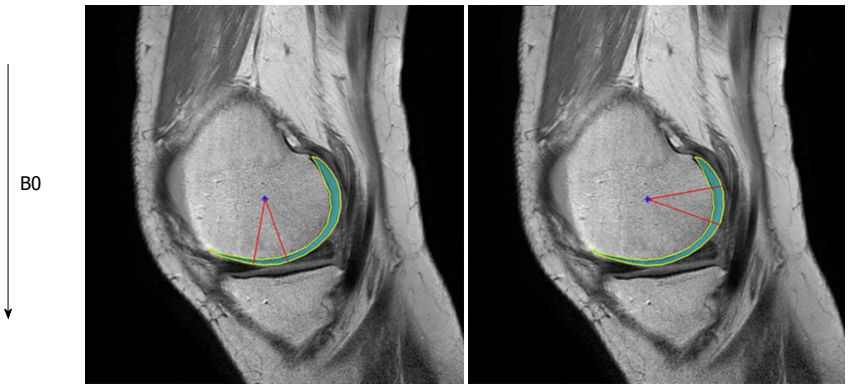


Figure 1 T2 and T1ρ relaxation time measurement. T2 and T1ρ relaxation times were measured in a range of -10 to 20 degrees for the distal condyle and 70 to 100 degrees for the posterior condyle. The angle 0 is defined along B0.

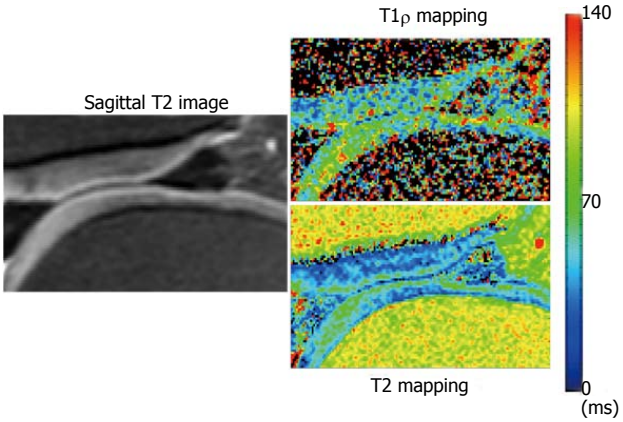


Figure 2 Example of sagittal fat suppressed proton density-weighted imaging, T1ρ mapping and T2 mapping.

and Masson's trichrome stain are demonstrated in Figure 3.

Table 2 shows the T2/T1ρ values and thickness of the cartilage in normal volunteers and advanced osteoarthritis patients. Although the difference of each cartilage thickness between normal volunteers and advanced OA patients was not observed, T2/ T1ρ values were significantly higher at the MPC in advanced OA patients compared to normal volunteers ($P < 0.05$). T2/T1ρ values also tended to be higher in advanced OA patients compared to normal volunteers at the MDC, LDC and LPC without significant difference.

DISCUSSION

Knee OA is a multifactorial disease with a significant population burden[1]. Novel strategies in the management of knee OA are based on early detection and minimally invasive procedures[11,19]. Certain patients with focal advanced knee OA may benefit from joint preservation strategies if remaining articular cartilage is healthy. In our study we aimed to assess whether normal appearing cartilage in advanced knee OA patients demonstrate depletion of proteoglycan and collagen content by T2/ T1ρ analysis, markers of early OA. We have demonstrated that although non-osteoarthritic portions of the femoral condyle in patients with advanced knee OA have similar morphologic characteristics compared to controls in routine MRI, there are significant changes on T2/T1ρ mapping that can measure differences on the biomolecular level.

Many *in vivo* studies have demonstrated an association between increased T2/T1ρ values and various stages of OA about the knee[12-15]. T1ρ values have been seen to increase with age, but are also higher in middle-aged populations with isolated patellofemoral and tibiofemoral compartment knee OA[13,14,20]. T1ρ relaxation times in particular may be elevated by as much as 30%-40% in patients with early knee OA[14]. Furthermore, Stahl *et al*[13] demonstrated that patients with asymptomatic knee OA have increased T2/T1ρ values in some compartments compared to healthy controls. These data are consistent with our findings that T2/T1ρ values are consistently higher in multiple compartments in patients with advanced OA compared to asymptomatic controls. By isolating pathologic samples with mild or near normal pathologic changes of articular cartilage we have demonstrated a subset of patients with mild arthritic changes. Li *et al*[12] have already shown significantly elevated T1ρ relaxation times in subcompartments of knee OA subjects where no prior morphologic changes were observed. This type of study demonstrates the utility of quantitative MRI sequences in detecting early biochemical changes within the articular cartilage matrix, but is limited to radiographic assessments alone. We have isolated not only radiographically similar, but pathologically similar cartilage samples to be used in this type of analysis.

This study agrees with multiple other publications that demonstrate the use of T2/T1ρ relaxation times for the early detection of knee OA[13,21,22]. The unique contribution is the comparison of normal or near normal imaging samples between cases and controls. Thuillier *et al*[23] examined patients with patellar-femoral pain but without radiographic evidence of knee OA and found significantly elevated T1ρ values in the lateral patellar cartilage compared to controls. Several other studies have also showed that focal cartilage defects identified on arthroscopy are correlated with elevated

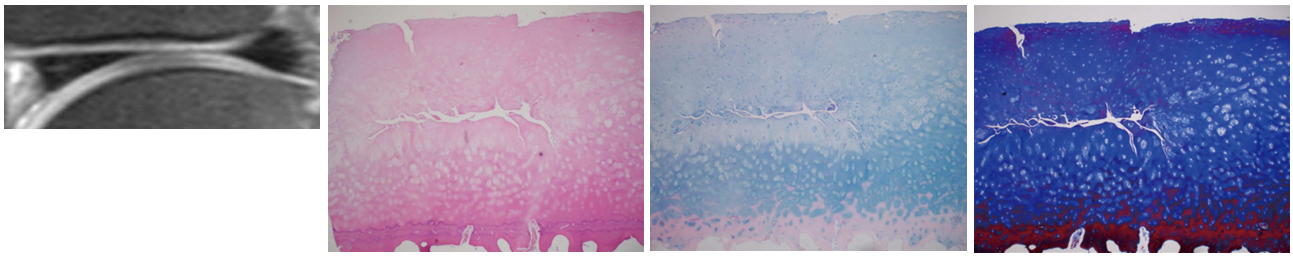


Figure 3 Example of normal thickness magnetic resonance imaging with corresponding hematoxylin and eosin, Alcian blue, and Masson trichrome stains. OA grade/stage/score in this case is 4/3/12, compatible with early OA. MRI: Magnetic resonance imaging; HE: Hematoxylin and eosin; OA: Osteoarthritis.

Table 1 Results of pathologic analysis of bone block and cartilage specimens

No.	Location	Grade	Stage	Score	Pathology comments
1	MDC	4	4	16	Superficial erosion, prominent vertical fissures and depletion of more than the upper 2/3 of proteoglycans by alcian blue staining
2	MPC	4	3	12	Focal erosion, a few small vertical clefts, depletion of the upper 1/2 to 2/3 of proteoglycans by alcian blue staining
3	LDC	3	4	12	Superficial fibrillation, small vertical clefts, minimal superficial depletion of proteoglycans by alcian blue staining
4	LDC	4.5	3	13.5	Deep erosion extending almost to bone and almost complete depletion of proteoglycans by alcian blue staining
5	MDC	4	3	12	Superficial erosion, prominent vertical and horizontal fissures and depletion of more than the upper 2/3 of proteoglycans by alcian blue staining
6	LPC	3.5	2	7	Focal superficial erosion almost complete depletion of proteoglycans by alcian blue staining
7	MPC	4	4	16	Erosion, focally deep and superficial depletion of proteoglycans by alcian blue staining over most of the surface, with complete depletion at region of deep erosion
8	LDC	3.5	4	14	Focal erosion and vertical fissures extending to mid zone with complete depletion of proteoglycans by alcian blue staining at site of fissures
9	LPC	3	4	12	Focal vertical fissures extending to mid zone with minimal depletion of proteoglycans by alcian blue staining
10	LDC	4.5	3	13.5	Focal deep erosion and superficial depletion of proteoglycans by alcian blue staining
Mean		3.82	3.45	13.09	

MDC: Medial distal condyle; MPC: Medial posterior condyle; LDC: Lateral distal condyle; LPC: Lateral posterior condyle.

MRI relaxation times[22,24,25]. We have similarly shown that morphologically normal articular cartilage, though adjoining osteoarthritic compartments of the knee, exhibit early changes in cartilage degeneration. These early changes include articular cartilage hydration, loss of proteoglycan content, thinning and loosening of collagen fibrils. While statistically significant changes were not observed in all compartments for this small sample size, the trends are readily apparent in all groups and notably significant in the MPC.

The utility of these sequences in joint preservation or replacement remains to be seen. T2 and T1ρ mapping have increasingly been applied with high fidelity to track outcomes after articular cartilage repair[26]. Studies have shown significant improvements in T1ρ relaxation times following microfracture and mosaicplasty, but values do not appear to ever return to baseline[26-28]. The question stands as to whether focal articular cartilage defects about the knee are amenable to preservation therapies if surrounding articular cartilage exhibits degenerative changes. No doubt there is a spectrum and diversity of cartilage injuries, and only a subset are arthritic in nature, but our data suggest that patients should be closely examined for early articular changes prior to such therapies. T2 and T1ρ mapping may have an important role in identifying which patients may benefit from preservation strategies and which are better candidates for joint replacement. Furthermore, these strategies may be used to develop personalized, systematic recommendations for patients with articular cartilage injuries.

This study is not without limitations. Only five patients undergoing TKA were recruited for the OA arm of the study. Although T2 and T1ρ were significantly higher in the posteromedial condylar segments, this study was underpowered to demonstrate statistically significant differences in the remaining condyles. We believe that a larger sample size would bolster our conclusions. Of note, there was a marked difference in age between the OA group and controls (70 years *vs* 28.9 years). Differences in T2 and T1ρ mapping may be confounded by physiologic changes with age alone, as previously mentioned. Although the concept of morphologically normal but biochemically impaired cartilage is valid, this observation may weaken the validity of our argument

Table 2 Comparison of T2/T1ρ values and cartilage thickness between the control cohort and advanced osteoarthritis patient

		Control (n = 20)	AOA (n = 5)	P[1]
MDC	T2-value[2]	52.23	64.9	0.524
	T1ρ-value	52.5	52.98	0.642
	T2-cartilage thickness[3]	6.13	5.38	0.461
	T1ρ-cartilage thickness	5.7	6.8	0.97
MPC	T2-value	46.83	59.3	0.016
	T1ρ-value	57.15	73.5	0.043
	T2-cartilage thickness	8.6	10.05	0.352
	T1ρ-cartilage thickness	8.7	8.93	0.938
LDC	T2-value	48.93	53.7	0.067
	T1ρ-value	55.85	62.55	0.371
	T2-cartilage thickness	6.58	6.4	0.654
	T1ρ-cartilage thickness	6.2	5.75	0.587
LPC	T2-value	44.2	50.8	0.218
	T1ρ-value	48.53	68.5	0.055
	T2-cartilage thickness	8.93	7.95	0.55
	T1ρ-cartilage thickness	8.5	9.15	0.601

[1]Mann-Whitney *U* test; [2]T2 and T1ρ values, measured in milliseconds; [3]Thickness, measured in pixels. AOA: Advanced osteoarthritis; MDC: Medial distal condyle; MPC: Medial posterior condyle; LDC: Lateral distal condyle; LPC: Lateral posterior condyle.

regarding joint preservation options. Furthermore, this is a cross-sectional design with no long-term follow-up as all OA patients underwent TKA. They also were not recruited according to degree or radiographic severity of disease and there is no long-term follow-up regarding symptom development in control subjects. However, there are lessons to be learned from this work that may help in the development of personalized treatments for OA and cartilage injuries.

In conclusion, our findings lend additional support to the use of T2 and T1ρ mapping in the diagnosis and management of OA of the knee. We have uniquely shown that even though cartilage is morphologically normal or near normal, cartilage degenerative changes exist in advanced OA patients. These early changes can be detected with T2 and T1ρ MRI techniques and consideration should be given to the use of these sequences in the early detection of OA.

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COMMENTS

Background

Characterized by the progressive loss of articular cartilage, osteoarthritis (OA) is one of the largest and fastest growing medical conditions worldwide. Significant damage to the collagen-proteoglycan matrix is believed to precede the loss of cartilage and consequent symptoms of knee OA. Among imaging techniques, magnetic resonance T1ρ has stood out as a high sensitivity option to detect these early changes in otherwise young, healthy joints.

Research frontiers

Prior studies have demonstrated increased cartilage T1ρ values, a surrogate of cartilage damage, in patients with knee OA. Specifically, T1ρ and T2 values are known to be elevated in asymptomatic, healthy subjects with early stage OA compared to individuals without focal lesions. The basic science foundation for the use of these techniques is now understood, but translating them into clinical practice is an area of current interest.

Innovations and breakthroughs

In recent years, novel strategies have been explored for the early detection of OA. Magnetic resonance T1ρ and T2 mapping has emerged as an excellent candidate for this endeavor. The authors have uniquely shown that even though cartilage is morphologically normal or near normal, cartilage degenerative changes exist in advanced OA patients. These early changes can be detected with T2 and T1ρ magnetic resonance imaging techniques and consideration should be given to the use of these sequences in the early detection of OA.

Applications

The authors' findings lend support to the use of T2 and T1ρ mapping in the diagnosis and management of OA of the knee. The results of this study suggest that asymptomatic individuals under consideration for knee joint preservation strategies may benefit from pre-procedure T2 and T1ρ analysis. Future studies should build upon their results to determine specific T2 and T1ρ parameters whereby joint preservation strategies are likely to fail.

Terminology

Standard T2 and lesser-known T1ρ magnetic resonance pulse sequences can be used as surrogates of cartilage damage in patients with knee OA. Specifically, T1ρ and T2 values are known to be elevated in asymptomatic, healthy subjects with early stage OA compared to individuals without focal lesions.

Peer-review

It is a well-written paper.

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