T1ρ Mapping of Subtalar Articular Cartilage in Patients with Ankle Osteoarthritis

Yuhei Maki1, Naoki Haraguchi1, Kota Asano1, Tatsuya Arimoto1, Yosuke Kano1, Suguru Mikami1, Satomi Kimura1, Gaku Fukumoto1, Takayuki Yamada3, Takuo Sato3, Atsushi Tsutaya4, Takashige Yoshida4, Koki Ota5, and Hisateru Niki2

(Received for Publication: September 16, 2021)

Abstract

Advanced osteoarthritis (OA) of the ankle is often accompanied by arthritic changes in the subtalar joint, and when arthrodesis is performed for ankle OA, the subtalar joint symptoms remain or even worsen. If the degree of subtalar cartilage degeneration can be quantified, prognosis can be predicted. T1ρ mapping has proven useful for identification of early cartilage degeneration. We hypothesized that T1ρ values of subtalar joint cartilage are higher (i.e., cartilage degeneration is greater) in patients with ankle OA without plain radiographic evidence of subtalar joint space narrowing and osteophytes than in healthy individuals. The T1ρ value of full thickness subtalar joint cartilage was measured on sagittal MR images obtained from 12 patients with ankle OA (3 with Takakura stage 3a disease and 9 with Takakura stage 3b disease) and from 12 healthy individuals. Imaging was performed with a 3.0 T MRI scanner, and PRIDE was used to construct T1ρ maps. A region of interest was set on the water-selective excitation image, which was projected onto the corresponding slice of the T1ρ mapping image to calculate the T1ρ value. The T1ρ value of the subtalar cartilage in patients with ankle OA (41.8 [39.8, 44.4] ms) did not differ significantly from that in healthy individuals (45.0 [37.0, 50.2] ms) (p=0.219 by Mann-Whitney U test). Our findings suggest that the T1ρ value of subtalar articular cartilage in patients with stage 3a or 3b ankle OA for whom conventional imaging reveals no OA changes does not differ significantly from that of healthy individuals.

Key words

T1ρ mapping, ankle osteoarthritis, subtalar articular cartilage

Introduction

Osteoarthritis (OA) is a chronic joint disorder characterized by degeneration of articular cartilage and synovitis1). The prevalence of symptomatic OA in the general adult population in the United States is 15%2). With the prevalence of ankle OA being lower than that of knee OA or hip joint OA, ankle OA accounts for 4.4% of all cases of symptomatic OA3). For patients with end-stage ankle OA, ankle arthrodesis or total ankle arthroplasty is usually performed. Ankle arthrodesis has a very good pain-relieving effect and is considered the gold standard for treatment of ankle OA. However, because such arthrodesis reduces the range of motion of the ankle, functional disability can result. Furthermore, the subtalar joint,
which is an adjacent joint, is burdened. Therefore, subtalar joint symptoms remain or worsen. If the subtalar joint is also affected by the advanced OA, tibiotalocalcaneal fusion may be performed. Many patients with end-stage ankle OA also have subtalar joint OA, but it is difficult to distinguish between ankle and subtalar joint symptoms before surgery. Also, if the subtalar joint OA is of a relatively early stage, radiographic evidence is sparse, and there is no index by which to evaluate the degree of cartilage degeneration. Therefore, a diagnostic imaging modality that can directly quantify the degree of cartilage degeneration is desired. If the degree of cartilage degeneration can be quantified, the prognosis can be determined, but to date, a method for non-invasively quantifying cartilage degeneration in the subtalar joint has not been established.

T1ρ magnetic resonance imaging (MRI) mapping is attracting attention as a new means of non-invasively quantifying the proteoglycan (PG) content in articular cartilage. T1ρ MRI is performed by application of a spin-lock pulse before the imaging sequence is obtained, and it quantifies the longitudinal relaxation of the target organ. The T1ρ value reflects the chemical exchange that occurs between the restricted motion protons and surrounding protons. The articular cartilage substrate consists mainly of water (60–80%), collagen (15%), and PG (9%) . Early OA is thought to be characterized by PG loss but little collagen degeneration. When PG is disrupted by cartilage degeneration, the proton exchange rate in cartilage increases, and the T1ρ value increases. The T1ρ value has been shown to correlate negatively with the PG concentration, and thus T1ρ mapping is useful for non-invasive evaluation of early OA. We thus acquire T1ρ images in all cases of ankle OA. We are aware, however, that T1ρ mapping has been used to assess cartilage degeneration mainly in the knee joint; few studies have focused on the ankle joint and subtalar joint.

We hypothesized that the T1ρ value of subtalar cartilage in patients with ankle OA is higher (reflective of cartilage degeneration) than that in individuals without ankle OA for this study. We believe this is the first study conducted to quantify degeneration of subtalar cartilage by T1ρ mapping.

Materials and Methods

Study subjects

Included in our study were 12 patients (5 men and 7 women) diagnosed with ankle OA between June 2013 and March 2022. Patients ranged in age from 37 to 78 years, and the disease was of stage 3a (n=3) or stage 3b (n=9). The patients were identified from our department’s patient database. Their ankle OA had been graded according to the Takakura classification system as modified by Tanaka et al on the basis of weight-bearing anteroposterior ankle radiographs. According to this system, stage 1 osteoarthritis involves no narrowing of the joint space but does involve early sclerosis and formation of osteophytes; stage 2 involves narrowing of the medial joint space; stage 3a involves obliteration of the medial joint space, with subchondral bone contact limited to the medial malleolus; stage 3b involves subchondral bone contact extending to the roof of the dome of the talus; and stage 4 involves obliteration of the whole joint space with complete bone contact. Criteria for inclusion in the study were as follows: (1) a diagnosis of primary varus ankle OA, (2) absence of subtalar joint space narrowing and osteophytes on a plain radiograph, (3) T1ρ mapping having been performed, and (4) age of 20 years or more. In addition, 12 healthy individuals (9 men and 3 women; 31.0 [26.8, 36.0] years of age) who, for the purpose of the study volunteered to undergo MRI including T1ρ mapping were included as control subjects. Criteria for their inclusion were as follows: (1) provision of written informed consent for their participation, (2) age of 20 years or more, and (3) absence of any complaints pertaining to the foot or ankle joint on the imaging side. This study was approved by the ethics committee at St. Marianna University School of Medicine (approval no. 5215).

Imaging protocol

MRI was performed with a 3-Tesla scanner (Ingenia 3.0T system or Achiwa 3.0T system, Philips Healthcare, Best, Netherlands) equipped with an 8-channel SENSE knee coil or dS Small Extremity coil (Philips Healthcare). Imaging was done with the ankle in neutral position when the dS Small Extremity coil was used or in plantar flexion position when the SENSE knee coil was used. Two sequences were acquired: a T1-weighted sagittal three-dimensional water-selective excitation (WATS-3D) sequence (repetition time/echo time [TR/TE] = 16 ms/5.2 ms, flip angle = 20 degrees, field of view = 14 cm, matrix = 400 × 400, slice thickness = 1.0 mm, and interslice gap = −0.5 mm) and a T1ρ-weighted turbo field echo sagittal sequence (spin-lock pulse amplitude = 500 Hz per pixel; spin-lock pulse time (TSL) = 1, 10, 20,
30, 40 ms; TR/TE = 5.6 ms/2.7 ms; flip angle = 35 degrees; field of view = 12 × 12 cm; matrix = 256 × 256; slice thickness = 2 mm; interslice gap = 0 mm; bandwidth = 615.8 Hz; number of excitations = 1. All imaging was begun between 5 pm and 6 pm.

**Postprocessing**

The T1ρ maps were reconstructed with use of the Philips Research Integrated Development Environment (PRIDE) software (Philips Medical Systems, Best, The Netherlands) written in an interactive data language (Research Systems, Inc., Boulder, CO, USA) according to the following mono-exponential fitting algorithm: 

\[ S (\text{TSL}) = S_0 \times \exp(-\text{TSL}/T1\rho) \]


where TSL is the spin-lock time, S is the signal intensity on the T1ρ-weighted image with a given TSL, and S₀ is the signal intensity when the TSL = 0. Images were analyzed with the use of Image J (NIH, Bethesda, MD, USA). A region of interest (ROI) was set on the T1-weighted sagittal 3D water-selective image, and this was projected onto the same slice of the T1ρ mapping image to determine the T1ρ value. Because the boundary between the cartilage on the talus side and the cartilage on the calcaneus side of the subtalar joint was not detectable on the image, the ROI was set to cover for both. A total of 83 ROIs were set on the images of ankle OA, and a total of 80 ROIs were set on the control images (Figure 1).

**Reproducibility of T1ρ value measurement**

Reproducibility of T1ρ value measurement was tested in 5 of the 12 cases of ankle OA. T1ρ was measured twice on each of the previously obtained images for each of the 5 patients (1 man and 4 women; age 66 [58–72] years) at an interval of about 3 weeks. An orthopaedic fellow (YM), spine surgeon (KA), and foot and ankle specialist (NH) set the ROIs and measured the T1ρ values. The relaxation time for T1ρ mapping at each ROI was measured 3 times by each examiner, and the mean times were determined.

**Statistical analyses**

Data are shown as median (25th percentile, 75th percentile) values. Reliability of ROI placement was tested by intraclass correlation coefficient (ICC) and its 95% confidence interval (95% CI). The ICCs were calculated from a mixed-effects model, with measurements as response variables, and samples, repeti-
tions, observers, and errors as random effects, and reliability was classified according to the Altman system as very good (0.81–1), good (0.61–0.8), moderate (0.41–0.6), fair (0.21–0.4), or poor (0.2). Age, sex, body mass index (BMI), disease stage, and T1ρ values were compared between the patients and healthy individuals, and differences were analyzed by Mann-Whitney U test or Fisher’s exact probability test, as appropriate. All statistical analyses were performed with EZR (Jichi Medical University Saitama Medical Center, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R Commander designed to add statistical functions frequently used in biostatistics. Significance was accepted at p<0.05.

Results

Subtalar MRI findings in the patients with ankle OA and the healthy individuals

WATS-3D showed no morphological cartilage damage in the subtalar joint or bone marrow edema of the subchondral bone in the patients with ankle OA. WATS-3D also showed no abnormalities in the healthy individuals.

Evaluation of reproducibility of T1ρ mapping

The coefficient of variation (CV, measurement error/overall mean) was 1.0%, and the ICC was 0.982 (0.732–1.000). Therefore, the reliability of T1ρ measurement was “very good.”

Characteristics of the total study subjects

Age, Sex, BMI, Takakura-Tanaka stage, and the T1ρ Value of each of the study subjects are shown on Table 1. Overall, age of the patients with ankle OA was 66.0 (57.8, 69.5) years, and that of the healthy individuals was 21.6 (19.2, 23.2) years, with the ankle OA patients being significantly older than the healthy individuals (p=0.0001). The sex ratio did not differ significantly between the ankle OA patients and the healthy individuals (p=0.214). BMI of the patients with ankle OA was 25.8 (24.0, 28.4) kg/m², and that of the healthy individuals was 21.6 (19.2, 23.2) kg/m², indicating that patients with ankle OA were significantly overweight (p<0.0001) (Table 2).

T1ρ value in the patients with ankle OA and in the healthy individuals

The T1ρ value of the subtalar joint in patients with ankle OA was 41.8 (39.8, 44.4) ms and did not differ significantly from that of the subtalar joint in the healthy individuals (45.0 [37.0, 50.2] ms) (p=0.219) (Table 2).

Discussion

The MRI T1ρ value is the time constant obtained from the longitudinal relaxation of the target organ when irradiated with a spin-lock pulse. Because the spin-lock pulse is of low frequency at several hundred Hz, it is possible to approach low-frequency molecular biological phenomena. The PG that retains water in the cartilage substrate exchanges protons bound to its protein side chain with protons in the surrounding bulk water, and this low-frequency level interaction is thought to affect the T1ρ relaxation time. Therefore, when the molecular structure of PG collapses for some reason, the water protons retained by PG are released into bulk water, the number of mobile protons in the cartilage substrate increases, and the proton exchange rate increases, resulting in an increased T1ρ value. Thus, T1ρ mapping can quantify change in the PG concentration in the extracellular matrix of cartilage substrates. Studies have shown the T1ρ value in patients with knee OA to be significantly higher than that in healthy individuals. Earlier studies of bovine articular cartilage subjected to cartilage trypsinization revealed loss of PG and corresponding increases in T1ρ values. Further, negative correlation has been found between the T1ρ value of the knee cartilage in patients with advanced knee OA and the amount of PG in specimens obtained at the time the patients underwent total knee arthroplasty. In addition, as noted above, there is PG degeneration but little degeneration of collagen structure in early-stage OA, so in patients with early-stage OA, the molecule structure breaks down and the water content increases in the cartilage matrix before symptoms appear and before the loss of cartilage is apparent in the images. In patients with knee OA, the T1ρ value was shown to be high in the region where morphological cartilage thinning was not observed on conventional MRI, and softening and swelling of the superficial cartilage was confirmed only by knee arthroscopy. Thus, calculation of the T1ρ value makes it possible to detect OA early in the disease process, i.e., before symptoms appear and before changes can be detected radiographically or by conventional MRI. Clinical application of T1ρ mapping will allow for identification of patients at high risk for development or progression of OA, in turn allowing for early intervention.
Table 1. Age, Sex, BMI, Takakura Stage, and T1ρ Value of the Individual Study Patients and Healthy Individuals

| Age (years) | Sex | BMI (kg/m²) | Takakura stage | T1ρ value (ms) |
|-------------|-----|-------------|----------------|----------------|
| Patients with ankle OA (n=12) |
| 72 | Male | 22.2 | 3b | 41.4 |
| 71 | Male | 24.2 | 3b | 44.6 |
| 37 | Male | 24.3 | 3a | 48.6 |
| 78 | Female | 28.2 | 3b | 40.3 |
| 59 | Female | 25.6 | 3a | 42.3 |
| 58 | Female | 22.2 | 3b | 38.2 |
| 66 | Male | 29.1 | 3b | 42.8 |
| 57 | Female | 29.1 | 3b | 35.6 |
| 66 | Female | 28.1 | 3b | 37.0 |
| 69 | Male | 23.4 | 3b | 40.6 |
| 66 | Female | 33.3 | 3a | 48.6 |
| 69 | Female | 26 | 3b | 44.3 |
| Healthy individuals (n=12) |
| 48 | Male | 23 | 47.9 |
| 39 | Male | 24.4 | 47.8 |
| 27 | Male | 21.5 | 50.7 |
| 32 | Male | 22.7 | 40.6 |
| 34 | Male | 23.4 | 41.3 |
| 26 | Female | 18.1 | 41.5 |
| 30 | Male | 21.6 | 42.2 |
| 26 | Male | 23.5 | 54.0 |
| 35 | Male | 19.2 | 37.0 |
| 29 | Male | 20 | 50.1 |
| 40 | Male | 19 | 38.0 |
| 26 | Female | 18.8 | 53.1 |

OA, osteoarthritis; BMI, body mass index

T2 mapping is also known as a non-invasive direct imaging technique that can be used to assess cartilage quantitatively. However, T2 mapping does not reflect the PG concentration; rather, it reflects the collagen concentration, so T2 mapping is considered inferior to T1ρ mapping for early detection of OA. In a study investigating the detectability of International Cartilage Repair Society grade 1 cartilage lesions, T2 mapping yielded 76.5% sensitivity and 81.6% specificity, whereas T1ρ mapping yielded 91.2% sensitivity and 89.5% specificity, with accuracy of T1ρ mapping being superior to that of T2 mapping.

Cases of varus-type ankle OA for which radiography and conventional MRI yielded no significant evidence of OA in the subtalar joint were included in our study. The Takakura-Tanaka classification system is widely used to stage varus-type ankle OA, with stages 1 to 4 representing increasing degrees of OA change seen on the weightbearing anteroposterior ankle radiograph. In cases of varus-type ankle OA, varus malalignment in relation to the tibial axis progresses as the disease stage progresses. Valgus inclination of the subtalar joint progresses through stage 3a, converting to varus position in stage 3b. The calcaneus is valgus with respect to the talus through stage 3a, converting to varus position in stage 3b. This change in inclination is known as the compensatory function of the subtalar joint, and breakdown of the compensatory mechanism leads to progression of the varus angulation after stage 3b. The relation between the compensatory function of the subtalar joint and progression of the subtalar OA is not clear, but as
Table 2. Age, Sex Ratio, BMI, and T1ρ Value of Study Patients with OA vs. Healthy Subjects

|                        | Patients with ankle OA (n=12) | Healthy individuals (n=12) | p Value       |
|------------------------|-------------------------------|-----------------------------|---------------|
| Age (years)            | 66.0 (57.8, 69.5)             | 31.0 (26.8, 36.0)           | <0.0001*      |
| Sex ratio (M:F)        | 5:7                           | 9:3                         | 0.214#        |
| BMI (kg/m²)            | 25.8 (24.0, 28.4)             | 21.6 (19.2, 23.2)           | <0.0001*      |
| T1ρ value (ms)         | 41.8 (39.8, 44.4)             | 45.0 (37.0, 50.2)           | 0.219*        |

OA, osteoarthritis; BMI, body mass index
Median (25th percentile,75th percentile) values are shown, unless otherwise indicated.
*by Mann-Whitney U test
# by Fisher’s exact probability test

The stage of the ankle OA progresses, mechanical stress on the subtalar joint could increase, which may lead to the progression of the subtalar joint OA. The subtalar joint OA would be even more pronounced after stage 3b, when the compensatory mechanism fails. Therefore, we hypothesized that the T1ρ value of the subtalar joint in cases of ankle OA is higher than that of healthy joints, but our hypothesis was not validated. Rather, little degeneration of the subtalar articular cartilage was found in our patients with stage 3a or 3b ankle OA and in whom no OA changes were detected by plain radiography and conventional MRI.

In cases of ankle OA, if early OA changes can be detected by T1ρ mapping and the degree of OA can be quantified, the prognosis can be predicted, and the appropriate surgery can be selected. For example, in cases in which the subtalar OA is not significant in terms of symptoms, radiographic findings, or conventional MRI findings, and if the presurgical T1ρ value is not high, i.e., cartilage degeneration is not pronounced, ankle fusion without subtalar joint arthrodesis can be considered. To the contrary, if the T1ρ value is high, i.e., cartilage degeneration is pronounced, a joint-preserving procedure, such as total ankle arthroplasty or lower tibial osteotomy, can be considered to avoid progression of subtalar OA. In cases involving severe OA of the subtalar joint, tibiotalo-calcaneal fusion may be indicated.

The major limitations of our study are that it was retrospective and the number of cases of ankle OA was small. Also, the greater mean age of patients in the ankle OA group vs. age of those in the control group may have affected the results. The older the knee joint cartilage, the higher the T1ρ value. This is thought to be due to age-dependent degeneration of knee articular cartilage and loss of PG. However, to date, there has not any report of a study conducted to analyze the relation between T1ρ values and age of healthy ankle and subtalar articular cartilage. The amount of PG in the ankle joint is considered not to correlate with age. This is because the ankle joint has an anatomically stable structure compared to that of the knee joint, and it possesses high biomechanical rigidity due to the large amount of PG in the cartilage substrate and to the fact that talar chondrocytes are highly resistant to catabolic stimuli. Therefore, the effect of age on the T1ρ value may be small even in the subtalar articular cartilage, with the subtalar joint being a more stable joint than the ankle joint, but this question remains for further study. The difference in sex ratio between our two study groups may also have affected our results. In addition, a high BMI is regarded as a risk factor for ankle OA, as it is for OA of other joints, and it has been reported that the higher BMI, the greater the probability that ankle OA will develop after 3 to 4 years. The BMI of our patients with advanced ankle OA was significantly
higher than that of our healthy subjects. This difference might have affected our study results, but if so, the $T1_\rho$ values obtained for our study patients should also have been statistically high, and they were not. By collecting more data on healthy persons in the future, it will be possible to make age- and weight-adjusted comparisons.

Because changes in the PG concentration in human articular cartilage result from various factors, the $T1_\rho$ value may not be specific to in vivo change in the PG content\textsuperscript{9}. All imaging performed on our study patients was initiated between 5 pm and 6 pm, but the load conditions were not uniform. Differences in patients’ metabolism and physical environments might have affected the water content in cartilage. In addition, it has been reported that the $T1_\rho$ value of articular cartilage decreases with increased load. When MRI was performed in healthy subjects and in patients with knee OA and a temporarily added 50% body weight load, the $T1_\rho$ value decreased in both groups, and it was speculated that this occurred because the load causes water to leak from the cartilage, proportionately increasing the PG concentration\textsuperscript{30}. In addition, from a 3D gait-based investigation into the relation between contact pressure and the contact area inside the normal knee joint and the $T1_\rho$ value, it was reported that the $T1_\rho$ value is low in the region where the contact pressure is high and a cyclic load is applied\textsuperscript{31}. Thus, it is possible that the $T1_\rho$ value obtained in our study was lower than the true $T1_\rho$ value due to the constant load on the subtalar cartilage in the patients with ankle OA. It will be necessary to investigate the relation between the $T1_\rho$ value and stages of ankle OA other than stage 3 and between the $T1_\rho$ value and other clinical indicators, such as radiographic evidence of the OA.

**Conclusion**

Our findings suggest that the $T1_\rho$ value of subtalar articular cartilage in patients with stage 3a or 3b ankle OA and for whom plain radiography and conventional MRI reveal no OA changes does not differ significantly from that of healthy individuals.

**Conflicts of Interest**

The authors have nothing to disclose.

**References**

1) Goldring MB, Goldring SR. Osteoarthritis. J Cell Physiol 2007; 213: 626–634.
2) Lawrence RC, Helmick CG, Arcnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 1998; 41: 778–799.
3) Cushmanahgan J, Dieppe P. Study of 500 patients with limb joint osteoarthritis. I. Analysis by age, sex, and distribution of symptomatic joint sites. Ann Rheum Dis 1991; 50: 8–13.
4) Takakura Y, Tanaka Y, Sugimoto K, et al. Long Term results of arthrodesis for osteoarthritis of the ankle. Clin Orthop Relat Res 1999; 361: 178–185.
5) Sheridan BD, Robinson DE, Hubble MJW, et al. Ankle arthrodesis and its relationship to ipsilateral arthritis of the hind- and mid-foot. J Bone Joint Surg Br 2006; 88: 206–207.
6) Wang YYJ, Zhang Q, Li X, et al. $T1_\rho$ magnetic resonance basic physics principles and applications. Quant Imaging Med Surg 2015; 5: 858–885.
7) Ross MH, Pawlina W. Histology: a text and atlas, 6th ed, Lippincott Williams & Wilkins, Philadelphia, 2011: 198–217.
8) Dijkgraaf LC, Bont LG, Boering G, et al. Normal cartilage structure, biochemistry and metabolism: a review of the literature. J Oral Maxillofac Surg 1995; 53: 924–929.
9) Duvvuri U, Goldberg AD, Kranz JK, et al. Water magnetic relaxation dispersion in biological systems: the contribution of proton exchange and implications for the noninvasive detection of cartilage degradation. Proc Natl Acad Sci USA 2001; 98: 12479–12484.
10) Li X, Majumdar S. Quantitative MRI of articular cartilage and its clinical applications. J Magn Reson Imaging 2013; 38: 991–1008.
11) Tanaka Y, Takakura Y, Hayashi K, et al. Low tibial osteotomy for varus-type osteoarthritis of the ankle. J Bone Joint Surg Br 2006; 88: 909–913.
12) Kanda Y. Investigation of the freely-available easy-to-use software “EZR” (Easy R) for medical statistics. Bone Marrow Transplant 2013; 48: 452–458.
13) Sepponen RE, Pohjonen JA, Sipponen JT, et al. A method for T1 rho imaging. J Comput Assist Tomogr 1985; 9: 1007–1011.
14) Mäkelä HI, Gröhn OH, Kettunen MI, et al. Proton exchange as a relaxation mechanism for T1 in the rotating frame in native and immobilized protein solutions. Biochem Biophys Res Commun 2001; 289: 813–818.
15) Li X, Ma CB, Link TM, et al. In vivo T(1rho) and T(2) mapping of articular cartilage in osteoarthritis of the knee using 3 T MRI. Osteoarthrits Cartilage 2007; 15: 789–797.
16) Carballido-Gamio J, Stahl R, Blumenkratz G, et al. Spatial analysis of magnetic resonance T1rho and T2 relaxation times improves classification between subjects with and without osteoarthritis. Med Phys 2009; 36: 4059–4067.
17) Akella SV, Regatte RR, Gougoutas AJ, et al. Proteoglycan-induced changes in T1rho-relaxation of articular cartilage at 4T. Magn Reson Med 2001; 46: 419–423.
18) Regatte RR, Akella SV, Borthakur A, et al. Proteoglycan depletion-induced changes in transverse relaxation maps of cartilage comparison of T2 and T1rho. Acad Radiol 2002; 9: 1388–1394.
19) Li X, Cheng J, Lin K, et al. Quantitative MRI using T1p and T2 in human osteoarthritic cartilage specimens: correlation with biochemical measurements and histology. Magn Reson Imaging 2011; 29: 324–334.
20) Nishioka H, Hirose J, Nakamura E, et al. T1p and T2 mapping reveal the in vivo extracellular matrix of articular cartilage. J Magn Reson Imaging 2012; 35: 147–155.
21) Witschey WRT, Borthakur A, Fenty M, et al. T1rho MRI quantification of arthroscopically confirmed cartilage degeneration. Magn Reson Med 2010; 63: 1376–1382.
22) Nishioka H, Hirose J, Nakamura E, et al. Detecting ICRS grade 1 cartilage lesions in anterior cruciate ligament injury using T1p and T2 mapping. Eur J Radiol 2013; 82: 1499–1505.
23) Hayashi K, Tanaka Y, Kumai T, et al. Correlation of compensatory alignment of subtalar joint to the progression of primary osteoarthritis of the ankle. Foot Ankle Int 2004; 294: 400–406.
24) Muehleman C, Margulis A, Bae WC, et al. Relationship between knee and ankle degeneration in a population of organ donors. BMC Med 2010; 8: 48. doi: 10.1186/1741-7015-8-48.
25) Chang SH, Yasui T, Taketomi S, et al. Comparison of mouse and human ankles and establishment of mouse ankle osteoarthritis models by surgically induced instability. Osteoarthritis Cartilage 2016; 24: 688–697.
26) Treppo S, Koepp H, Quan EC, et al. Comparison of biomechanical and biochemical properties of cartilage from human knee and ankle pairs. J Orthop Res 2000; 18: 739–748.
27) Eger W, Schumacher BL, Mollenhauer J, et al. Human knee and ankle cartilage explants: catabolic differences. J Orthop Res 2002; 20: 526–534.
28) Lateef S, Golightly YM, Renner JB, et al. A cross-sectional analysis of radiographic ankle osteoarthritis frequency and associated factors: the Johnston County Osteoarthritis Project. J Rheumatol 2017; 44: 499–504.
29) Jaleel A, Golightly YM, Alvarez C, et al. Incidence and progression of ankle osteoarthritis: the Johnston County Osteoarthritis Project. Sem Arthritis Rheum 2021; 51: 230–235.
30) Souza RB, Kumar D, Calixto N, et al. Response of knee cartilage T1rho and T2 relaxation times to in vivo mechanical loading in individuals with and without knee osteoarthritis. Osteoarthritis Cartilage 2014; 22: 1367–1376.
31) Rossom SV, Smith CR, Zevenbergen L, et al. Knee cartilage thickness, T1p and T2 relaxation time are related to articular cartilage loading in healthy adults. PLoS One 2017; 12: e0170002. doi: 10.1371/journal.pone.0170002.