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T2 mapping in the quantitative evaluation of articular cartilage changes in children with hemophilia: A pilot study

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ABSTRACT

Importance: Joint disease affects more than 90% of severe hemophiliacs. Early diagnosis is critical in preventing hemophilic arthritis. Magnetic resonance imaging (MRI) enables visualization of early arthropathic changes and plays an important role in treatment.

Objective: To evaluate the role of T2 mapping in detecting early cartilage lesions in the knee and ankle joints of children with hemophilic arthropathy.

Methods: Target joints of 15 male patients with clinically confirmed moderate or severe hemophilia were evaluated with MRI. In addition to routine MRI protocols (T1WI, T2_FFE, T2_SPAIR, PDW_TSE), T2 mapping was used to evaluate the articular cartilage of target joints.

Results: The mean T2 value of the distal femoral cartilage was 46.72 ± 10.94 ms, which is higher than the reported age-matched normal value (40.27 ± 3.50 ms). The mean T2 value of the proximal tibial cartilage was 45.60 ± 8.82 ms, which is higher than the reported normal value (31.15 ± 1.86 ms). Four examined joints (two ankles, two knees) showed normal morphology with no abnormal signal on routine MR sequences. However, T2 mapping showed locally increased T2 values in the cartilage, along with uneven color scales.

Interpretation: The quantitative assessment method of T2 mapping might be helpful to early diagnosis for articular cartilage lesions. It might be a potential tool for early assessment of cartilage changes and quantification of lesion's severity for hemophilia joint.

KEYWORDS
Magnetic resonance imaging, Articular cartilage, Hemophilia

INTRODUCTION

Hemophilia is a recessive X-linked genetic bleeding disorder, with a prevalence of 1 to 5 per 10 000 live births.[1] The disorder can be divided into hemophilia A (factor VIII deficiency) and hemophilia B (factor IX deficiency) and may be further classified according to clotting factor level as severe (less than 1%), moderate (1%–5%), or mild (> 5%).[2] According to the World Federation of Hemophilia, there are 100 000–130 000 hemophilia patients in China. Joint bleeding is one of the main features of hemophilia. Recurrent joint bleeding can lead to synovial and osteochondral lesions, with ankylosis and malformation in severe cases. Joint involvement occurs in more than 90% of patients with severe hemophilia and can seriously affect quality of life.

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With the application of refined clinically graded prevention and treatment strategies worldwide, morphological changes in the joints of pediatric hemophilia patients have been dramatically delayed or avoided. However, does normal joint morphology indicate no damage? How can we grade and quantify the severity of articular lesions that have progressed to osteochondral destruction? These questions need to be addressed with medical imaging in patients with hemophilic arthropathy (HA). Magnetic resonance imaging (MRI) is recognized as the gold standard for the comprehensive evaluation of joint changes. Currently, MRI is the optimal imaging method for the noninvasive observation of articular cartilage.[3] T2 mapping technology quantitatively measures transverse relaxation and has been widely used in studies of cartilage disease. The purpose of this study was to detect early lesions in hemorrhagic joints and evaluate the severity of HA in children with hemophilia by using the T2-mapping technique; this technique may provide an early and sensitive evaluation measure for the further diagnosis and treatment of HA.

METHODS

Ethical approval of the study protocol

The study protocol was approved by the Ethics Committee of Beijing Children's Hospital (BCH; Beijing, China, [2014] -Y-011-C).

Case selection

Fifteen pediatric patients (mean age, 12.27 ± 3.39 years; range, 8−17 years) with laboratory-confirmed moderate or severe hemophilia in February 2015 were enrolled in this study. In each child, a target joint with the largest number of joint bleeds was selected for MRI examination. Accordingly, seven knee joints and eight ankle joints were examined. Clinical diagnosis was hemophilia A in 13 cases and hemophilia B in two cases; disease severity was moderate in four cases and severe in 11. Coagulation factor concentrations were below 4% in all patients. A total of 30 articular surfaces (both proximal and distal surfaces in 15 joints) were examined. All 15 patients had experienced hemorrhage of the skin, muscles, craniofacial region, and/or buttocks before presentation and had a clear history of joint bleeding; the first joint bleeding occurred in the ankle in two cases, in the elbow in two cases, in the toe joints in one case, and in the knee in 10 cases. The age at first bleeding ranged from 12 to 72 months (28.7 ± 8.33 months). The frequency of bleeding was one to four times per month. The patients with other joint disease, like juvenile idiopathic arthritis, rheumatoid arthritis, dermatomyositis were excluded to this study.

Examination method

All MRI scans were performed with Philips Achieva 3.0T TX MR system (Best Netherlands). Knee joints were examined with an 8-channel knee coil, and ankle joints with an 8-channel head coil. Patients were positioned in the feet-first supine position. Sponges were used to stabilize the joints. All knee and ankle joints were scanned with routine sequences and a T2 mapping sequence. The routine sequences included sagittal T1WI, T2_FFE, T2_SPAIR, and PDW_TSE. The T2 values of knee and ankle cartilage were measured with T2 mapping; T2-mapping pseudocolor images of articular cartilage were created at a post-processing workstation. Five echoes were acquired in the sagittal plane, with a TE value of 13−78 ms and scan time of 5 min. The scanned images were transmitted to the post-processing workstation for further processing. The scanning parameters are shown in Table 1.

Image processing

The original images were transmitted to an IntelliSpace Portal 4.1 workstation for post-processing. Sagittal images were automatically divided into three regions: A (anterior), B (central), and C (posterior); T2 values were obtained for each region. For the knee joints, the T2 values of the distal femoral cartilage and proximal tibial cartilage were measured; for the ankle joints, the T2 values of the distal tibial cartilage and talar dome cartilage were measured. More specifically, the divisions between cartilage and bone cortex and between cartilage and articular surface were manually drawn on the pseudocolor image; the software then automatically generated three equally divided regions A, B, and C, along with the corresponding T2 values in these regions. Cartilage T2-value curves were

TABLE 1 Main MRI scanning parameters for knee articular cartilage

Sequences	TR(ms)	TE(ms)	FOV(mm)	Slice thickness(mm)	Slice spacing(mm)	Matrix	NSA	Scan time
Sagittal T_2_FFE	422	12	160	3	0.5	304*253	2	2 min 54 s
Sagittal T_2W_SPAIR	4000	60	160	3	0.5	244*256	2	3 min 44 s
Sagittal PDW_TSE	4817	30	160	3	0.5	360*276	2	3 min 08 s
Sagittal T_1W_TSE	500	15	160	3	0.5	292*272	1	2 min 06 s
Sagittal T_2 mapping	1700	13,26,39,52, 68,75,61,70	140	2.5	0.25	480*480	1	5 min 08 s

MRI, magnetic resonance imaging; TR, repetition time; TE, echo time; FOV, field of view; NSA, number of signal accept

also generated for different regions. All measurements were made by two trained radiologists and the agreement between the observers was tested.

The MRI acquisition protocols for articular cartilage recommended by the International Cartilage Repair Society[4] were applied to grade the sagittal T2_FFE and T2W_SPAIR sequences in the knee joint with the most prominent lesion. Defect grades were as follows: grade 0, normal cartilage with smooth surface and even signal and without abnormal subchondral bone signal; grade 1, smooth cartilage surface, with locally high signal in subchondral bone; grade 2, minor tears of less than one-half the thickness of the cartilage layer; grade 3, lesions with deep crevices of more than one-half the thickness of the cartilage layer; and grade 4, full-thickness cartilage tear with exposure of subchondral bone. One senior radiologist reviewed the images to verify the agreement of the measurements made by the two radiologists in this study.

Statistical analysis

Statistical analysis was performed with SPSS 17.0. Measurement data are expressed as mean ± standard deviation; count data are expressed as numbers and percentages. Cohen's kappa statistic was calculated to measure agreement between the two radiologists. values above 0.75 were interpreted as excellent agreement, 0.40 to 0.75 as fair to good, and below 0.40 as poor. The T2 values in regions A, B, and C in the articular cartilage of knee and ankle joints were analyzed with ANOVA; the T2 values of the same regions were compared between the upper and lower articular surfaces of the knee and ankle joints with paired *t* tests. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Cohen's kappa value for the measurements obtained by the two radiologists was 0.84 ($P < 0.05$), indicating good agreement. The measured T2 values of articular cartilage are shown in Table 2. of the T2 values in the three regions revealed the following F values: 0.008 for the distal femoral cartilage, 0.181 for the proximal tibial cartilage, 0.157 for the distal tibial cartilage, and 2.806 for the talar cartilage (all P values > 0.05). Paired *t* tests revealed significant differences in the T2 values between the proximal and distal articular surfaces in region C (posterior region) of ankle ($P = 0.011$); no such differences were seen in regions A or B in ankle and no differences were seen in all regions in knee ($P > 0.05$).

The mean T2 values of both the distal femoral cartilage (46.72 ± 10.94 ms) and proximal tibial cartilage (45.60 ± 8.82 ms) of the knee joints were higher than those age-matched normal values (40.27 ± 3.50 ms and 31.15 ± 1.86 ms, respectively) reported in the literature.[15] Because of the limited number of cases ($n = 7$), we only described the measurement results and did not make statistical analysis with the normal reference values reported in the literature. The mean T2 values of the proximal and distal articular surfaces of the ankle joints were 37.51 ± 8.20 ms and 41.58 ± 6.82 ms, respectively; reference values have not been reported for pediatric patients in this age group. In four cases (two ankles and two knees), the examined joints showed normal morphology and routine MR sequences did not reveal any abnormal signal. However, T2 mapping of the cartilage showed increased T2 values in local areas, along with uneven color scales.

According to the criteria of the International Cartilage Repair Society,[4] four cases were grade 0 (Figure 1), one was grade 1, three were grade 2 (Figure 2), six were grade 3, and one was grade 4 (Figure 3). In the four patients with grade 0 cartilage (two ankle joints and two knee joints), the T2_FFE and T2_SPAIR sequences were normal, with no obviously abnormal signal; however, the color scale of the cartilage was uneven.

DISCUSSION

Pathological changes in HA patients

HA is mainly characterized by spontaneous or minor post-traumatic intra-articular hemorrhage. A small initial bleed can be completely absorbed without leaving any residue; however, chronic repeated heavy bleeding will lead to a series of major pathological changes in the synovium, articular cartilage, and subchondral bones. In severe cases, ankylosis and deformity may develop. Synovial hyperplasia and cartilage damage are key pathological changes in HA patients; bleeding typically occurs repeatedly in one or two joints, which are termed

TABLE 2 T2 values of articular cartilage in different regions and the reference values (mean ± SD)

Region	Region A (ms)	Region B (ms)	Region C (ms)	Mean (ms)	Reference value[15] (ms)
Distal femoral cartilage ($n = 7$)	46.46 ± 8.86	47.13 ± 12.31	46.56 ± 11.63	46.72 ± 10.94	40.27 ± 3.50
Proximal tibial cartilage ($n = 7$)	45.56 ± 5.63	47.19 ± 14.72	44.04 ± 5.10	45.60 ± 8.82	31.15 ± 1.86
Distal tibial cartilage ($n = 8$)	38.85 ± 8.57	36.81 ± 9.43	36.88 ± 6.59	37.51 ± 8.20	-
Talar dome cartilage ($n = 8$)	36.80 ± 5.78	43.08 ± 9.78	44.85 ± 4.89	41.58 ± 6.82	-

-, no reference value is available.

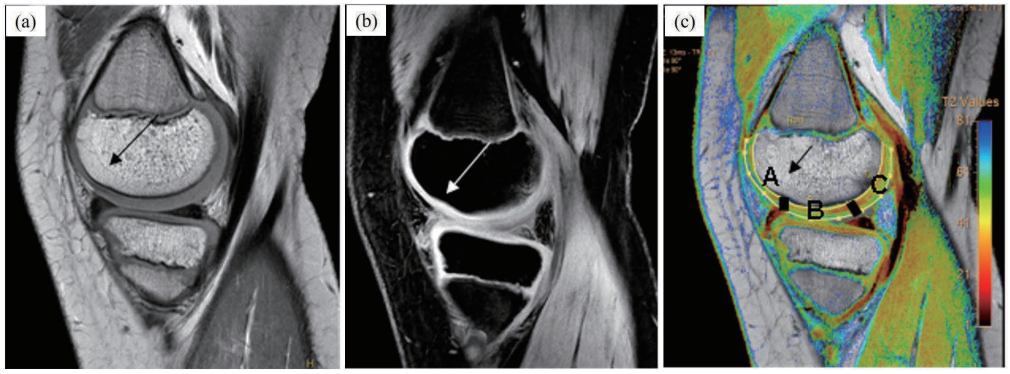

FIGURE 1 Images from a 10-year-old boy with moderate hemophilia (knee joint, grade 0). (a) T1WI and (b) T2W_FFE sequences show normal articular cartilage morphology and signal (black and white arrows). (c) T2-mapping pseudocolor image shows uneven pseudocolor in distal femoral cartilage and increased T2 value in region A (black arrow).

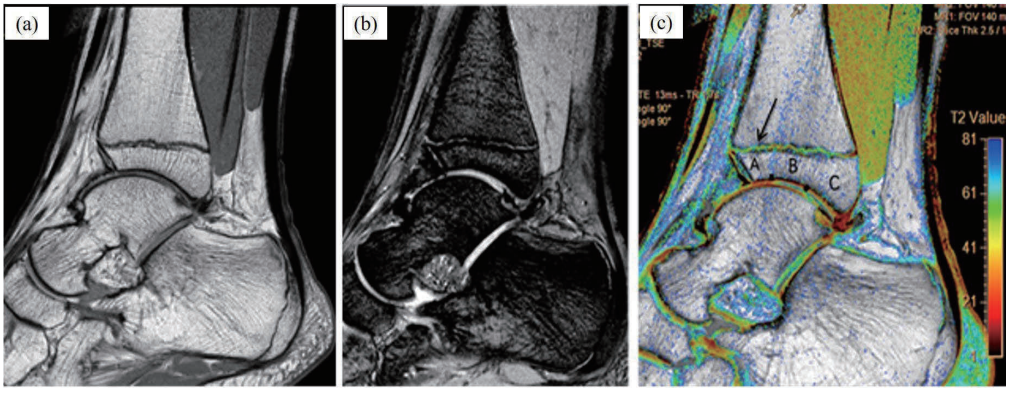

FIGURE 2 Images from a 12-year-old boy with moderate hemophilia (ankle joint, grade 2). (a) T1WI and (b) T2W_FFE sequences show articular cartilage thin at the A area, (c) T2-mapping pseudocolor image shows uneven pseudocolor in distal tibial cartilage (black arrow).

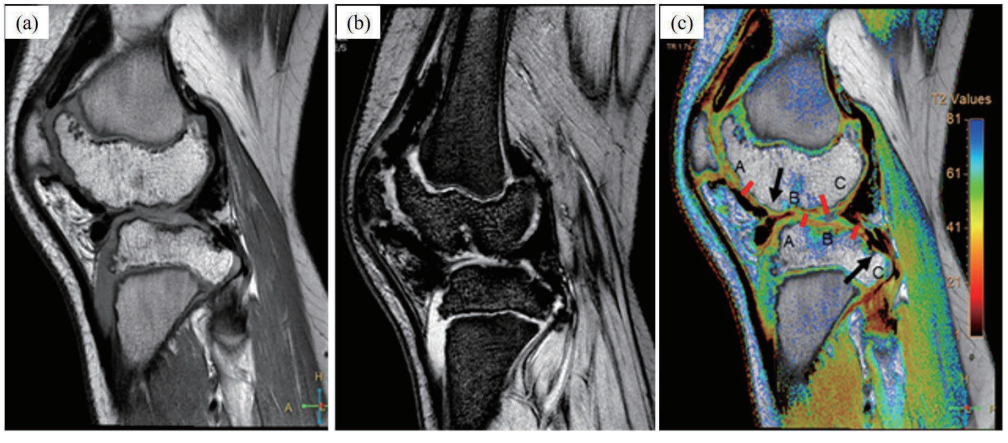

FIGURE 3 Images from 9-year-old boy with severe hemophilia (knee joint, grade 4). (a) T1WI and (b) T2W_FFE sequences show articular bone damage, with sawtooth-like changes. The articular cartilage is unevenly thinned, with partial defects. (c) T2-mapping pseudocolor image shows complete defects of local cartilage in region B of distal femoral cartilage and region C of proximal tibial cartilage, with exposed bone cortex. Grade 4 cartilage (black arrow).

target joints (those with recurrent bleeding three or more times within 3 months).[5] Many studies have shown that intraarticular hemorrhage caused by lack of coagulation factors triggers changes in the synovium, cartilage, and subchondral bone.[6] The age at first hemorrhage and the frequency of bleeding depend on the degree of clotting factor deficiency. Joint hematoma occurs in toddlers (1−5 years of age), with a high frequency of bleeding at 1.2 to 2 years of age; however, plain X-ray films often show no obvious bone abnormality before 3 years.[7] Pathological changes differ among individual patients because of differences in the interval from disease onset to clinical

presentation and in the frequency and severity of joint bleeding.[8] Joint hemorrhage occurs more often in joints with heavy activity and pressure; the damage to cartilage and bone progresses with age.[9] According to the literature, the most common target joints are the knees, ankles, and elbows.[10] Therefore, in this study, knee and ankle joints were examined as target joints.

Application of T2 mapping

T2 mapping has been applied clinically as an MRI technique to evaluate the biochemical composition of cartilage. MRI T2 values quantify changes in the components of articular cartilage. This technique has high clinical value in the diagnosis and monitoring of early cartilage injury.[11,12] T2 mapping uses multilevel, multi-echo spin echo sequences to generate the original images, which are post-processed at the workstation to produce pseudocolor images. The T2 value of the cartilage is obtained from measurements in the region of interest. Once a spatial distribution map of the cartilage T2 value is obtained, the articular cartilage can be quantitatively assessed. Factors affecting the T2 value in the cartilage mainly include collagen fiber anisotropy, collagen concentration, and water content. The T2 value is a quantitative, noninvasive indicator of cartilage degeneration. When collagen and proteoglycan levels in the cartilage decrease, the signals on T2-weighted images increase; this increase can be further enhanced by cartilage edema. Therefore, changes in the cartilage matrix and cartilage edema can both be reflected in T2 mapping.[13,14] It is widely recognized that an increase in cartilage T2 relaxation time is associated with damaged cartilage microstructure.[15] Many studies have investigated the role of T2 mapping of articular cartilage and concluded that changes in T2 values and T2-mapping pseudocolor maps can reveal the morphology and early damage of articular cartilage.[16,17] In the present study, four patients had normal joint morphology and no abnormal signal in routine MR sequences of the cartilage. However, T2 mapping revealed locally increased T2 values, along with uneven color levels, suggesting the presence of early cartilage lesions in these HA patients.

Value of T2 mapping in the assessment of hemophilic arthropathy

A study that measured T2 values of knee articular cartilage in a same-age cohort found that the difference in the mean T2 values between femoral and tibial cartilage was approximately 10 ms; the mean T2 value of the distal femoral cartilage was higher than that of the proximal tibial cartilage.[15] In the present study, the T2 values in the proximal and distal articular cartilages of the knee were similar and the mean T2 value of distal femoral and proximal tibial were 6 ms and 14 ms higher than reported age-matched normal value. This finding indicates that the proximal tibial cartilage might be more severely affected than the distal femoral cartilage, which may be explained by the fact that the proximal tibia is the weight-bearing articular surface.

T2 values did not significantly differ among the three cartilage regions (ipsilateral articular surfaces A, B, and C) in this study. Although the pathogenic mechanisms of joint disease remain unclear, and it has been reported that early cartilage damage in HA patients starts in the central region of the joint and gradually extends to the surrounding area.[18] In the present study, the T2 values in the anterior, central, and posterior regions were similar, which might have resulted from frequent bleeding in the target joints, varied degrees of articular cartilage defects (in 10 cases), and severe articular cartilage damage.

The articular cartilage should be smooth, continuous, blue, and should have even signals on the post-processed color images.[15] In four of our 15 patients, although the T2_FFE appearance and T2_SPAIR signal of the articular cartilage were normal, the T2 value was increased and the color levels of the pseudocolor images were uneven, indicating the presence of early cartilage damage before morphological abnormalities or signal changes could be seen on routine MR sequences.

It has been reported that bleeding frequency and age are moderately correlated with osteochondral changes on MRI; irreversible osteochondral lesions markedly increase with increasing age and bleeding frequency, causing more damage to the joints.[19,20] As the earliest and most popular imaging method, X-ray examination is widely used to assess pathological changes such as joint destruction, bone cyst formation, narrowing of the joint space caused by cartilage defects, and joint deformation. In the early 1980s, X-ray imaging was adopted by the World Hemophilia Alliance as a tool for hemophilia. However, because the scope of X-ray assessment is limited to the stage of osteoarticular destruction, it cannot be used to assess the nature and degree of cartilage lesions and cannot directly display articular cartilage, and thus is not suitable for observing early joint lesions.

Advances in medical imaging and clinical treatments in the past 30 years have led to improved therapeutic options for patients with hemophilia.[21] Prophylactic treatment slows the progression of joint lesions secondary to joint bleeding more than on-demand treatment or lack of treatment; ultimately, these patients may have no clinically evident joint bleeding. However, subclinical bleeding may still occur in some pediatric patients. Because there is no joint swelling, pain, or joint dysfunction in these patients, T2 mapping is recommended for patients without positive findings on routine sequences, including T2_FFE and T2_SPAIR, to increase diagnostic accuracy and avoid delayed treatment. Although arthroscopy is the gold standard for diagnosing articular cartilage lesions, this invasive technology is obviously not feasible in children

with hemophilia. Several imaging methods have been used to evaluate HA in recent years;[22,23] however, they have not been widely applied in the evaluation of early cartilage changes. As shown in the present study, T2 mapping is a valuable tool for detecting early cartilage lesions in children during their physical development. With short scan time, powerful post-processing software, and high operability,[11] T2 mapping is clinically feasible and can provide an objective basis for early diagnosis.[24] In our current study, T2 values were locally increased in four patients with normal morphology of knee and ankle articular cartilage, suggesting that these pediatric patients should protect their weight-bearing joints during daily activities and sports activities to avoid or slow down cartilage damage.

Unfortunately, our study was limited by its small sample size. Our conclusions will be further validated in future studies. As we know T1p is also a sensitive bio-marker compared with T2 mapping. But the MRI machine used in this study had no T1p software, so we used T2 mapping for assessment method.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Feldman BM, Funk S, Lundin B. Musculoskeletal measurement tools from the International Prophylaxis Study Group (IPSG). *Haemophilia.* 2008;14 (Suppl 3):162-169.
2. Hilgartner MW. Current treatment of hemophilic arthropathy. *Curr Opin Pediatr.* 2002;14:46-49.
3. Kong Y, Qiang Y, Dong B, Zhang L. The value of 3DWATS and T2 mapping on the measurement of normal adult male knee joint cartilage thickness. *J Clin Radiol.* 2013;32:1626-1629. (In Chinese)
4. Brittberg M, Winalski CS. Evaluation of cartilage injuries and repair. *J Bone Joint Surg Am.*2003;85-A Suppl 2:58-69.
5. Forsyth AI, Rivard G, Valentino LA, et a1. Consequences of intra-articular bleeding in haemophilia: science to clinical practice and beyond. *Haemophilia.* 2012;18(Suppl 4):S112-119.
6. Lundin B, Manco-Johnson ML, Ignas DM, et al. An MRI scale for assessment of haemophilic arthropathy from the International Prophylaxis Study Group. *Haemophilia*. 2012;18:962-970.
7. Pergantou H, Platokouki H, Matsinos G, et al. Assessment of the progression of haemophilic arthropathy in children. *Haemophilia.* 2010;16:124-129.
8. Chen P, Chen X, Zhou X, Xu L. MRI features of hemophilic arthropathy. *Radiol Pract.* 2007;22:731-733. (In Chinese)
9. Sun S, Zhang L, Yang R, Sun H, Han Z. Clinical and radiological analysis of 101 hemophilic arthropathy cases. *Clin Med China.* 2006;22:326-330. (In Chinese)
10. Kilcoyne RF, Nuss R. Radiological assessment of haemophilic arthropathy with emphasis on MRI findings. *Haemophilia.* 2003;9(Suppl 1):57-63.
11. Kim HK, Shiraj S, Anton CG, Horn PS, Dardzinski BJ. Age and sex dependency of cartilage T2 relaxation time mapping in MRI of children and adolescents pediatric imaging. *AJR Am J Roentgenol.* 2014;202:626-632.
12. Ho-Fung VM, Jaramillo D. Cartilage imaging in children current indications, magnetic resonance imaging techniques, and imaging Findings. *Radiol Clin North Am.* 2013;51:689-702.
13. Nissi MJ, Toyras J, Laasanen MS, et al. Proteoglycan and collagen sensitive MRI evaluation of normal and degenerated articular cartilage. *J Orthop Res.* 2004;22:557-564.
14. Watrin-Pinzano A, Ruaud JP, Cheli Y, et a1. T2 mapping: an efficient MR quantitative technique to evaluate spontaneous cartilage repair in rat patella. *Osteoarthritis Cartilage*. 2004;12:191-200.
15. Lv Y, Chen S, Jiang S, Gong M, Feng X. MR T2 relaxation time measurement of normal knee articular cartilage in different age: Initial study and clinical significance. *J Clin Radiol.* 2011;30:1170-1173. (In Chinese)
16. Mosher TJ, Zhang Z, Reddy R, et al. Knee articular cartilage damage in osteoarthritis: analysis of MR image biomarker reproducibility in ACRIN-PA 4001 multicenter trial. *Radiology.* 2011;258:832-842.
17. Mamisch TC, Trattnig S, Quirbach S, Marlovits S, White LM, Welsch GH. Quantitative T2 mapping of knee cartilage: differentiation of healthy control cartilage and cartilage repair tissue in the knee with unloading−initial results. *Radiology.* 2010;254:818-826.
18. Roosendaal G, Lafeber FP. Blood-induced joint damage in haemophilia. *Semin Thromb Hemost.* 2003;29:37-42.
19. Zhang N, Peng Y, Wu R, Doria AS, Liu Y. Value of International Prophylaxis Study Group (IPSG) magnetic resonance imaging scale system in the evaluation of hemophiliac arthropathy joint changes in children. *J Capital Med Univ.* 2013;34:342-347. (In Chinese)
20. Wu R. Diagnosis and management of hemophilia in children. *J Appl Clin Pediatr.* 2012;27:1214-1216. (In Chinese)
21. Zhang N, Wu R, Peng Y. Multi-modal imaging evaluation for hemophilic arthropathy in children. *Chin J Pract Pediatr*. 2017;1:47-50. (In Chinese)
22. Li M, Ge Y, Wang L, et al. Comparation of multiple imaging in detection of arthropathies in patients with haemophilia. *Chin J Radiol.* 2012;46:912-916. (In Chinese)
23. Zhang N, Peng Y, Wu R. Value of high frequency ultrasound in assessment the changes of haemophiliac arthropathy in children. *Chin J Ultrasonogr.* 2014;23:59-61. (In Chinese)
24. Link TM, Li X. Establishing compositional MRI of cartilage as a biomarker for clinical Practice. *Osteoarthritis Cartilage.* 2018;26:1137-1139.

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