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ORIGINAL ARTICLE

T2 mapping magnetic resonance imaging of cartilage in hemophilia

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Abstract

Background: In hemophilia, recurrent hemarthrosis may lead to irreversible arthropathy. T2 mapping MRI may reflect cartilage changes at an earlier reversible stage of arthropathy as opposed to structural MRI.

Objectives: To evaluate interval changes of T2 mapping compared with the International Prophylaxis Study Group (IPSG) structural MRI scores of ankle cartilage in boys with hemophilia receiving prophylaxis.

Methods: Eight boys with hemophilia A (median age, 13; range, 9-17 years), 7 age- and sex-matched healthy boys (controls, median age, 15; range, 7-16 years). A multiecho spin-echo T2-weighted MRI sequence at 3.0T was used to obtain T2 maps of cartilage of boys with hemophilia and controls. Structural joint status was evaluated using the IPSG MRI score.

Results: T2 relaxation times of ankle cartilage increased significantly over time in both persons with hemophilia and controls (P = .002 and P = .00009, respectively). Changes in T2 relaxation time strongly correlated with changes in IPSG cartilage scores (r_s = 0.93 to r_s = 0.78 [P = .0007 to P = .023]), but not with changes in age (P = .304 to P = .840). Responsiveness of T2 relaxation times were higher than that of IPSG cartilage scores, with standardized response means >1.4 for T2 mapping in all regions-of-interest compared with 0.84 for IPSG cartilage scores. Baseline T2 relaxation time strongly correlated with timepoint 2 IPSG cartilage score (r_s = 0.93 to r_s = 0.82 [P = .001 to P = .012]) and T2 relaxation time (r_s = 0.98 to r_s = 0.88 [P = .00003 to P = .004]) changes in most regions-of-interest.

Conclusion: T2 mapping shows sensitivity to biochemical changes in cartilage prior to detectable damage using conventional MRI, offering potential for early detection of bleed-related cartilage damage in boys with hemophilia.

KEYWORDS
ankles, articular, biomarkers, cartilage, hemarthrosis, hemophilia A, International Prophylaxis Study Group MRI scale, joints, magnetic resonance imaging, T2 mapping

Essentials

- Late diagnosis leads to irreversible cartilage damage due to joint bleeds in hemophilia.
- T2 mapping magnetic resonance imaging (MRI) may predict future arthropathy progression.
- T2 mapping MRI reflects cartilage changes consistent with clinical joint health scores.
- T2 mapping MRI indicates cartilage damage prior to conventional MRI showing prognostic potential.

1 | INTRODUCTION

Hemophilia is a rare hereditary disease affecting approximately 400,000 individuals worldwide [1]. Recurrent bleeding into joints leads to chronic, painful, and disabling arthropathy [2], primarily occurring in patients with moderate or severe hemophilia. The resultant hemophilic arthropathy is caused by recurrent episodes of hemarthrosis in which synovial bleeding into the joint space leads to iron deposition in the joint, causing synovial inflammation. The subsequent cartilage degradation is thought to occur due to the presence of inflammatory enzymes from the inflamed synovium [3] or directly via damage to the cartilage by iron-catalyzed destructive oxygen metabolites [4] which results in irreversible damage to the articular cartilage [5].

Optimal management of persons with hemophilia and a severe bleeding phenotype is the administration of hemostatic agents administered on a regular basis ("prophylaxis") with the goal of preventing both subclinical and clinically overt bleeding into muscles and joints, thus preserving excellent long-term musculoskeletal health [6]. However, access to prophylaxis is limited by the high cost of replacement therapy and is not available to persons with hemophilia in low and some middle income countries. Of note, even in countries with reliable access to full-dose prophylaxis, many persons with hemophilia and a severe bleeding phenotype experience clinically significant bleed-related arthropathy over time, especially involving the ankles [7]. Causes of failure of prophylaxis are several fold and include lack of adherence to the prescribed prophylaxis regimen [8] and, likely in some cases, subclinical bleeding [9,10]. Given this background, there is a need for early detection of cartilaginous damage to better guide management of persons with hemophilia and a severe bleeding phenotype.

Conventional radiography enables a late diagnosis of hemophilic arthropathy as it cannot directly image cartilage, thus detecting only bone changes. Cartilage damage may be inferred based on joint space narrowing [11]. Although cartilage damage can be assessed to some extent using ultrasound [12,13], magnetic resonance imaging (MRI) is recognized as the reference standard for detection and quantitation of cartilage damage [14].

In normal cartilage, the proteoglycan molecule with its negatively charged glycosaminoglycan chains attracts water into the extracellular matrix. T2 mapping is a noninvasive MRI technique used to calculate the T2 relaxation times of tissues and display them on a parametric map. Unlike anatomic T1 and T2 imaging that is limited in terms of quantitative evaluation of degenerative changes in articular cartilage, T2 mapping is capable of detecting changes in water content, and in the orientation of the collagen fibers in the cartilage qualitative and quantitatively [15–18]. Because of its sensitivity to changes in the chemical composition and structure of the cartilage, T2 mapping MRI can serve as an image biomarker of cartilage degeneration [19,20], demonstrating potential as a viable tool for early detection of arthropathy in the hemophilia population [21,22].

Previous studies have shown that increased T2 relaxation times correlate with age [23,24] and with increased cartilage degradation of persons with hemophilia [21,25], rheumatoid arthritis [26,27], juvenile idiopathic arthritis [28], and osteoarthritis [29–31]. T2 mapping is thought to be capable of identifying arthropathic cartilage changes prior to clinical presentation of symptoms [32], as patients with osteoarthritis have shown increased T2 relaxation times years before the onset of macroscopic cartilage lesions [29].

We hypothesized that T2 mapping MRI is sensitive to early cartilage degradation occurring prior to currently detectable changes on conventional MRI in children and adolescents with hemophilic arthropathy, allowing detection at an earlier stage of arthropathy. In this study, we assessed T2 relaxation times of ankle cartilage of persons with hemophilia and compared them to healthy joints longitudinally. Through observing functional cartilage changes at an earlier stage compared with current structural imaging methods, T2 mapping MRI has the potential to identify early cartilage damage and thus inform treatment strategies such as intensification of prophylaxis that might limit or even prevent ongoing bleed-related cartilage and bone damage in persons with hemophilia and a severe bleeding phenotype.

2 | METHODS

Research ethics board approval was granted by our institution to conduct this study. Written informed consent was obtained from all persons with hemophilia or their parents or guardians and all healthy volunteers prior to participation in this study.

2.1 | Research design

The study cohort consisted of consecutive patients who had hemophilia and healthy control volunteers who underwent their baseline T2 mapping MRI examinations as part of another study of our group that prospectively acquired data from June 2012 to October 2014 [22]. Therefore, baseline data for the current study were obtained retrospectively based on a convenience sample. Subsequently, amended

TABLE 1 MR imaging parameters of the study protocol.

Sagittal T2 sequence		Coronal GRE sequence	
Manufacturer	Siemens	Manufacturer	Siemens
Model	Prisma Fit	Model	Prisma Fit
Power	3.0 Tesla	Power	3.0 Tesla
Matrix size	384 × 384	Matrix size	384 × 384
Resolution	0.5 × 0.5 × 3.0 mm	Resolution	0.5 × 0.5 × 3.0 mm
Echo train	3	Echo train	3
Repetition time	1000 ms	Repetition time	600 ms
Echo time	9.6/19.2/28.8 ms	Echo time	12.0/24.0/36.0 ms
Slide thickness	3.0 mm	Slide thickness	3.0 mm
Field of view	20 x 20 cm	Field of view	20 x 20 cm
Bandwidth	295.00 Hertz/pixel	Bandwidth	240.00 Hertz/pixel
Flip angle	90/180 degrees	Flip angle	20 degrees
Scan time	3:28 min	Scan time	3:12 min

research ethics board approval was granted for the investigators to contact patients and control subjects who underwent baseline MRI examinations and offer participation in a prospective extension of the study in which follow-up T2 mapping MRI examinations were performed 5 to 9 years after their baseline MRI examination. The rationale for the proposed interval of time between the baseline and follow-up MRI examinations was based on the results of a prior randomized controlled trial of persons who had hemophilia A and received prophylaxis vs on demand treatment [9]. That study showed that with a time interval of at least 4.5 years between the baseline and follow-up MRI examinations, 93% of patients in the prophylaxis group and 55% of patients in the episodic-therapy group revealed normal index-joint structure on anatomic MRI findings. Therefore, to maximize the likelihood of obtaining interval changes between the 2 MRI examinations a minimum interval of 5 years was proposed.

2.2 | Patients

Patients were enrolled into the study if they were aged 7 to 17 years, a diagnosis of hemophilia A, and were followed in the pediatric hemophilia treatment center of our institution in Toronto, Canada. All subjects were required to have a history of prior ankle bleeds. The ankle with the greatest number of joint bleeds was imaged.

2.3 | Healthy controls

The control group of the study consisted of healthy boys with ages ranging between 7 and 17 years, similar to the group of patients, who read the announcement posted by our group searching for volunteers for the baseline T2 mapping MRI examination. Control subjects were required to have no prior history of bleeding into their ankles or musculoskeletal disorders that could result in arthropathy such as juvenile idiopathic arthritis, muscular dystrophy, neuropathic arthropathy, and other disorders.

The study ankle was randomly selected.

2.4 | Clinical information

The total number of bleeds prior to the MRI examination for the study was recorded based on the *patients' electronic records*.

2.5 | Image acquisition

Patients underwent MRI of the ankle (tibia-talus) on dorsal decubitus. Structural (gradient-echo) and quantitative (T2-weighted multi-echo spin-echo) MR images were obtained in sagittal and coronal planes at 3.0 Tesla (Siemens Prisma Fit MR scanner, Siemens). Relevant imaging parameters used for T2 mapping MRI data analysis can be found in Table 1. Anatomic imaging parameters used for interpretation of MR images as it related to scoring according to the International Prophylaxis Study Group (IPSG) MRI scoring system [33] were described elsewhere [22]. A head coil overlying the joint of interest was used, and no sedation or contrast agent was administered to the participants. Acquired MR images were transferred onto Picture Archiving Communication Systems (PACS, General Electric) at the end of the examination for future data analysis and interpretation.

2.6 | Data analysis

Anatomic MR imaging assessments were conducted by a pediatric musculoskeletal radiologist with >15 years of experience after

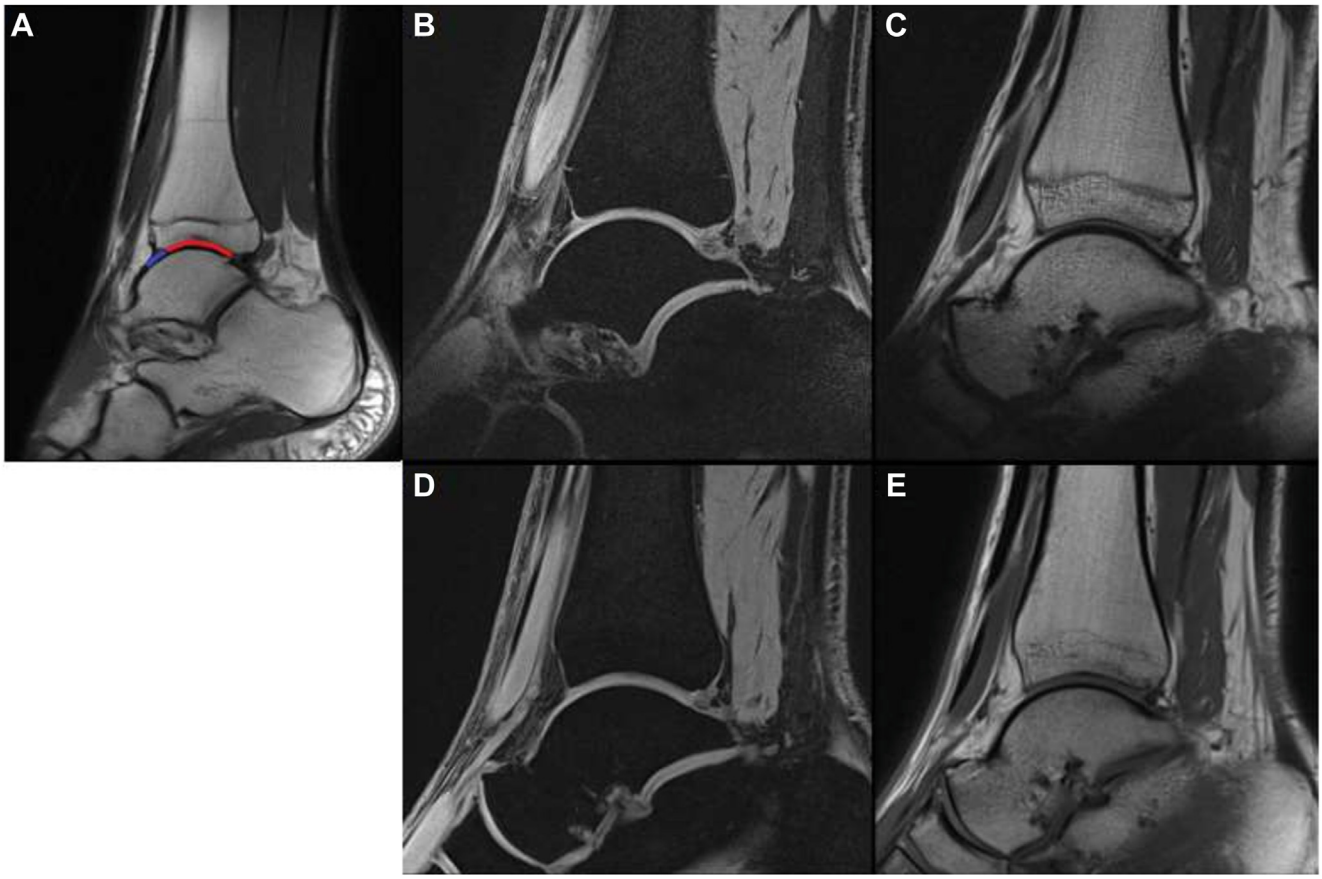

FIGURE 1 Regions-of-interest used to calculate T2 relaxation times and example of healthy cartilage showing no progression. (A) Weight-bearing (red) and non–weight-bearing (blue) regions of the ankle (tibia-talus) that were used for calculation of T2 relaxation values have been superimposed to the distal tibial/proximal talus cartilage complex on a sagittal MRI T2 map of a 17-year-old subject with hemophilia A. (B–E) Sagittal T1 volumetric interpolated breath-hold examination and corresponding sagittal T2 map (echo times of 9.6/19.2/28.8 ms) of the left ankle of a healthy volunteer of age 16 and 24 years old at timepoints 1 (B, C) and 2 (D, E) demonstrate persistent uniform articular cartilage of the distal tibia and proximal talus over a period of 8 years. T2 relaxation times at the tibiotalar joint for timepoints 1 and 2 were 50.4 and 68.9 ms, respectively.

training (A.S.D.) using the IPSG MRI scoring system [33] blindly to any clinical or laboratory information about patients. All data were deidentified and unique study identification numbers were assigned to each patient. The IPSG MRI scale encompasses 0 to 17 scores including osteochondral (0-8 scores) and soft tissue (0-9) domains. Anatomic MR images were previously stored on a PACS workstation.

Concerning T2 mapping MR imaging assessments, the operators (B.A.B., H.M.) correlated sagittal images for T2 mapping with corresponding coronal structural MR images (gradient echo sequence) to determine out of all sagittal images the single image lying halfway from the joint's edge to its midline that would serve as the region-of-interest (ROI) for T2 mapping analysis following a methodology previously described [18]. The operators were blinded to the hemophilia vs control status of MRI examinations for cases with no joint abnormalities. However, they could not be blinded to the joint status of MRI examination if abnormalities were visible on the scan. The data analysis was independently conducted by the operators on a serial basis, unblinded to the order of scanning of cases, using the sagittal plane for assessment. Some investigators may argue that knowing that the series of images belongs to a single patient may create a bias that can cause incorrect assumptions, for example overestimating progression of imaging findings in patients with known pathology [34]. Nevertheless, previous studies have shown that the approach in which readers have the ability to view all timepoint images for the corresponding patient simultaneously and with knowledge of their chronologic order is both more sensitive to change and has a greater reliability [35,36]. A workstation using a home-designed MATLAB software was employed for analysis. One of the operators (B.A.B.) analyzed the data again using the same methodology 1 month after the first analysis, blinded to his initial results.

Two ROIs were assessed in each joint under assessment: weight bearing and nonweight bearing (Figure 1A). Both weight bearing and nonweight-bearing cartilage regions were examined. Weight bearing ROIs were defined as the cartilage between the points at which the distal tibia cartilage is in closest proximity to the proximal talus cartilage, extending the entire width of the cartilage between the tibia and the talus bone cortex. Nonweight bearing regions of the ankle were defined as the anterior cartilage of the proximal talus due to the talus' limited rotation. For this ROI, cartilage extending from the end of the weight bearing region to as far as possible anteriorly was

TABLE 2 Baseline and follow-up clinical and anatomic MRI characteristics of study subjects.

										IPSG MRI Score 1				IPSG MRI Score 2			
Case #	Age 1	Age 2	Interval time	Age 1st bleed	Age start prophylaxis	Acute/Chronic	Severity	Inhibitors	*N* Bleeds	Total	Osteochondral	Cartilage	HJHS 1	Total	Osteochondral	Cartilage	HJHS 2
1	12-13	21-22	9	7	4	Chronic	Severe	No	6	4	0	0	3	7	6	2	N.A.
2	16-17	23-24	7	6	1	Chronic	Severe	No	100	1	0	0	6	8	5	2	9
3	10-11	17-18	7	10	6	Acute	Severe	No	7	7	0	0	10	6	3	3	4
4	9-10	16-17	7	6	10	Chronic	Severe	No	5	2	0	0	8	0	0	0	7
5	12-13	17-18	5	9	6	Chronic	Severe	No	10	11	4	2	5	11	7	3	7
6	14-15	22-23	8	6	5	Chronic	Severe	No	4	0	0	0	6	0	0	0	N.A.
7	15-16	21-22	6	14	N.A.*	Acute	Mild	No	4	5	0	0	N.A.	1	0	0	N.A.
8	17-18	22-23	5	17	1.5	Chronic	Severe	No	0	1	0	0	5	3	0	0	2

Acute, clinical suspicion of an acute joint bleed; Age 1, age range at timepoint 1 (in years); age 1st bleed, age at the 1st bleed (in years); Age 2, age range at timepoint 2 (in years); Age start prophylaxis, age at the start of prophylaxis (in years); Cartilage, IPSG MRI cartilage degradation score (range 0-4); Chronic, history of previous study joint bleeds; HJHS, Hemophilia Joint Health Score (version 2.1); interval time, interval of time between MRI examinations at timepoints 1 and 2; IPSG, International Prophylaxis Study Group; N Bleeds, lifetime number of study joint bleeds prior to visit 1; N.A., not available; N.A.*, on demand treatment; Osteochondral, IPSG MRI osteochondral score (cartilage loss + bone erosions + subchondral cysts, range 0-8); Total, total IPSG MRI score (soft tissue + osteochondral, range 0-17).

TABLE 3 T2 relaxation times for subjects with hemophilia and healthy controls.

	Hemophilia (mean T2 relaxation times ± SD, ms)		Controls (mean T2 relaxation times ± SD, ms)	
Region of interest	Timepoint 1	Timepoint 2	Timepoint 1	Timepoint 2
Lateral WB	58.0 ± 14.9	85.5 ± 31.3	51.5 ± 4.2	64.6 ± 7.9
Lateral non-WB	39.9 ± 8.2	78.7 ± 29.8	46.0 ± 8.2	61.0 ± 10.0
Medial WB	55.0 ± 15.4	81.6 ± 30.4	44.7 ± 5.7	58.3 ± 7.4
Medial non-WB	34.2 ± 8.6	62.7 ± 27.3	39.4 ± 3.6	52.1 ± 5.3

WB, weight bearing.

considered. A calibration session was conducted prior to data analysis for standardizing ROIs for T2 mapping analysis between the operators and the experienced radiologist. The user was blinded to all patient information concerning demographics and results of other examinations. If an ROI could not be measured due to lack of or excessively damaged cartilage, the measurement was excluded from the analysis. T2 relaxation times of manually selected ROIs were compared with those of a previous cross-sectional study from our group encompassing the same patient population to ensure consistency of measurements.

2.7 | Statistical analysis

All statistical analyses were conducted using SPSS (v. 26, IBM, Armonk, United States) or SAS (v. 9.4, SAS Institute, Cary, United States) software.

Inter- and intrarater reliability of our T2 mapping measurements in this study was calculated using the intraclass correlation coefficient (ICC).

Spearman's correlation coefficient (r_s) was used to determine the strength of correlation between interval changes in T2 relaxation times and changes in both age and IPSG cartilage score. It was also used to quantify the association between baseline (timepoint 1) and timepoint 2 IPSG cartilage score, timepoint 2 T2 relaxation time, change in IPSG cartilage score, and change in T2 relaxation time.

Paired samples *t*-test was used to determine the significance of T2 relaxation time increases over time, and the independent samples *t*-test was used to compare differences in the change in T2 relaxation times between hemophilic and healthy groups over time and between baseline T2 relaxation times of IPSG-progressing persons with hemophilia and controls. Although the same inclusion criteria for age was applied to patients and control subjects of the study, no age-matching statistical analysis was conducted comparing patients to control subjects.

Standardized response mean (SRM) was used to measure responsiveness of T2 mapping and IPSG cartilage scores. SRM is the average difference divided by the SD of the differences between the paired measurements. SRM values of >0.8 represent large changes, ≤0.8 and >0.5 moderate, and ≤0.5 and >0.2, small [37].

P values ≤ .05 were considered statistically significant. Normality of T2 relaxation times was confirmed using the Shapiro–Wilk test.

3 | RESULTS

3.1 | Patient and healthy control groups

Out of the larger cohort of subjects who underwent the baseline T2 mapping MRI examination only 8 out of 28 (29%) boys who had hemophilia and 7 out of 21 (33%) healthy control subjects accepted to undergo a follow-up T2 mapping MRI examination. Some follow-up visits were booked in 2021, during the COVID pandemic, affecting the recruitment. In addition, due to the study design, many patients scanned with T2 mapping MRI as adolescents in our institution became adults (aged ≥18 years) by the time participation in a second MRI scan was inquired and could not be contacted either because they left the city, province or country, or were no longer available or interested in participating in the study.

All study patients who had hemophilia were undergoing prophylaxis during the duration of the study.

Eight boys with hemophilia (all type A) were imaged at 2 different timepoints with a median interim interval of 7 years (range, 5-9). In the group of patients who had hemophilia, the median age at first visit was 13 years (range, 9-17) and it was 21 years (range, 16-23) at the second visit. Median IPSG cartilage scores were 0 (range, 0-2) and 1 (range, 0-3) for the 2 visits, respectively. As a control group, 7 healthy boys were imaged at 2 different timepoints with a mean interim time of 8 years (range, 4-9). In the control group the mean age at first visit was 15 years (range, 11-16) and it was 21 years (range, 15-24) at the second visit. Detailed patient demographic characteristics are shown in Table 2. Note is made of the fact that Table 2 shows a relative lack of correlation between number of lifetime hemarthrosis at the time of the baseline MRI and degree of cartilage damage according to structural IPSG scores at the follow-up MRI.

3.2 | Changes in T2 relaxation time reflect changes in IPSG cartilage score

As a measure of intra- and interrater reliability, the intraclass correlation coefficient (ICC) was 0.92 (95% CI = 0.82, 0.96) and 0.82 (95%

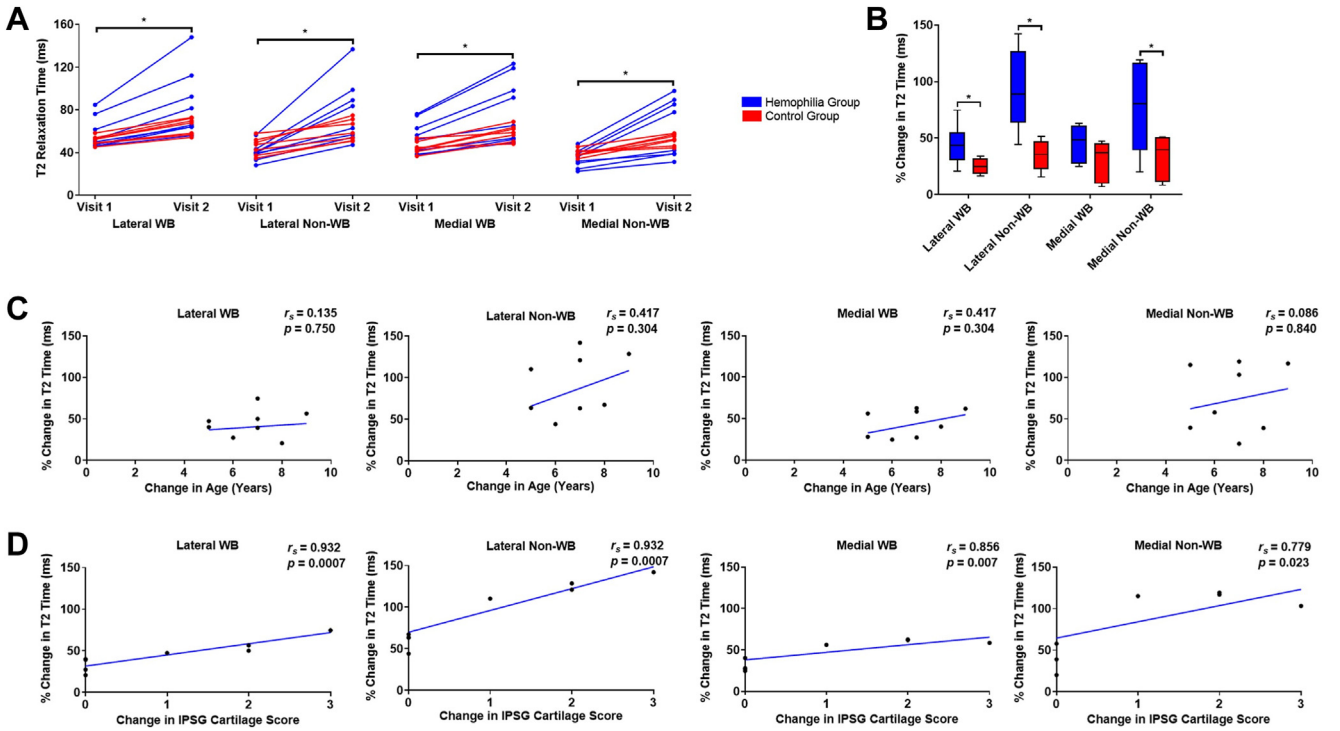

FIGURE 2 T2 relaxation time reflects degradational cartilage changes over time. (A) T2 relaxation times at first and second timepoints for all persons with hemophilia (blue) and healthy controls (red). A single asterisk indicates statistical significance at $P < .05$ of increase over time. (B) Changes in T2 relaxation times over time in persons with hemophilia (blue) and healthy controls (red). A single asterisk indicates statistical significance at $P < .05$. (C) Correlations between change in age and interval change in T2 relaxation time for persons with hemophilia in all regions-of-interest. (D) Correlations between change in IPSG cartilage score and interval change in T2 relaxation time for persons with hemophilia in all regions-of-interest. IPSG, International Prophylaxis Study Group; WB, weight bearing.

CI = 0.62, 0.92), respectively, indicating high consistency of measurements within and across raters.

T2 relaxation times of weight bearing and nonweight bearing ROIs are summarized in Table 3. Mean T2 relaxation times were significantly longer for both persons with hemophilia and healthy controls at their timepoint 2 examinations compared with their baseline (timepoint 1) examinations in all ROIs (P = .002 to P = .00009), showing a broad increase in T2 relaxation times over time (Figure 2A). We further examined differences in the magnitude of change in T2 relaxation times experienced between persons with hemophilia and healthy controls. Persons with hemophilia showed a significantly greater increase over time in T2 relaxation times for all ROIs except the medial weight bearing region (P = .0008 to P = .0684) (Figure 2B).

To determine the contributions of both age and cartilage degradation to the increasing T2 relaxation times, we evaluated the correlation between these factors and the interval change in T2 relaxation time. Interval changes in T2 relaxation times failed to show statistically significant positive correlations with changes in age (Figure 2C) in this pilot study. However, increasing T2 relaxation times correlated strongly with increases in IPSG cartilage scores in all ROIs (r_s = 0.9322 to r_s = 0.7790 [P = .0007 to P = .023]) (Figure 2D).

Qualitatively, a healthy control undergoing physiologic functional cartilage changes over 8 years had no cartilage damage at timepoint 1 visible by conventional MRI, as expected, and had T2 relaxation times of 50.4 and 68.9 ms at timepoints 1 and 2, respectively (Figure 1). A subject with hemophilia demonstrating progression of cartilage damage over 7 years had cartilage damage at timepoint 1 visible by conventional MRI (Figure 3). This subject had greater T2 relaxation times compared with the control subject of 75.0 and 119.0 ms at timepoints 1 and 2, respectively, and a notably increased change in T2 relaxation time between timepoints. Interestingly, a second person with hemophilia showing progression of cartilage damage over 5 years showed no cartilage damage visible by conventional MRI at timepoint 1 (Figure 4). However, T2 relaxation times and change in T2 relaxation times were similar to that of the previous person with hemophilia, with T2 relaxation times of 62.8 and 98.2 ms at timepoint 1 and 2, respectively.

In addition to assessing the ability of T2 mapping to reflect changes in IPSG cartilage score, we also investigated the sensitivity to change (responsiveness) of T2 relaxation times. As a measure of responsiveness, T2 mapping had a much greater SRM for all ROIs of different regions of the ankle cartilage assessed compared with IPSG cartilage scores (Figure 5A). SRM values of >0.8 represent large changes relative to SD, ≤0.8 and >0.5 moderate, and ≤0.5 and >0.2, small [37]. While IPSG cartilage scores had an SRM of 0.84, T2 mapping exceeded 1.40 in all ROIs.

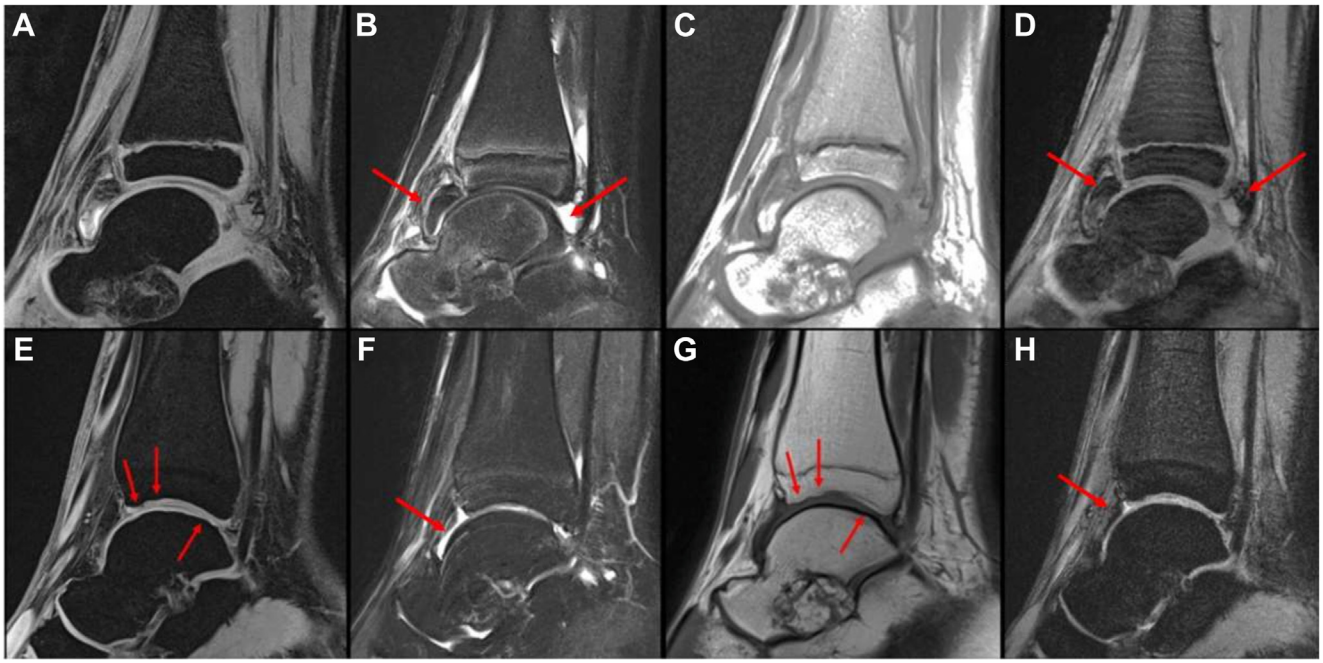

FIGURE 3 Example of interval development of cartilage damage not visible by conventional MRI at timepoint 1. Sagittal T1 volumetric interpolated breath-hold examination and corresponding sagittal SPectral Attenuated Inversion Recovery (STAIR) T2, T2 map (echo times of 9.6/19.2/28.8 ms), gradient recalled MR images of the right ankle of a boy with hemophilia of age 10 and 17 years old at timepoints 1 (A–D) and 2 (E–H). Structurally over time, there was interval partial thinning and irregularity of the articular cartilage involving the anterior distal tibia and at a lesser extent, talar dome (arrows, E, G) over >50% of the articular surface, score 2. In addition, early erosive changes involving <50% of the articular surface are noted, score 1. Concerning soft tissues, mild joint effusion and hemarthrosis (arrow, score 1, F) and residual synovial hypertrophy (score 1) and hemosiderin deposition (score 1, H) are noted at timepoint 2 (E–H), as opposed to severe hemarthrosis (arrows, score 3, B) and moderate synovial hypertrophy (score 2) and hemosiderin deposition (arrows, score 2, D) noted at timepoint 1 (A-D). Cartilage International Prophylaxis Study Group (IPSG) MRI scores at the tibiotalar joint for timepoints 1 and 2 were 0 and 3, respectively, whereas weight bearing cartilage T2 relaxation times at the tibiotalar joint for timepoints 1 and 2 were 75.0 and 119.0 ms, respectively.

3.3 | Baseline T2 predicts cartilage degradation over time

We further investigated the potential of T2 mapping as a predictive tool of future cartilage damage. When our cohort was stratified into groups based on progression of cartilage damage as assessed by the IPSG cartilage score, persons with hemophilia showing progression over time had significantly longer baseline T2 relaxation times in the weight bearing regions than the control group (P = .0004 to P = .007) (Figure 5B). Additionally, 3 of the 4 (75%) persons with hemophilia that showed progression over time began with an IPSG cartilage score of zero, indicating that at baseline measurement, they had no visible cartilage degradation by anatomic MRI. Our data revealed a high predictive power of baseline T2 relaxation time for future cartilage degradation as reflected by both IPSG cartilage scores and later T2 relaxation times. First, although the number of samples was small (N = 4 data points) higher baseline T2 relaxation times (*x-axis* of graph, Figure 5C) were strongly associated with increased IPSG cartilage scores at timepoint 2 (r_s = 0.93 to r_s = 0.82 [P = .001 to P = .012]) (*y-axis* of graph, Figure 5C). Based on the hypothesis that changes in T2 relaxation times reflect structural changes in IPSG cartilage scores, baseline T2 relaxation times (*x-axis* of graph, Figure 5D) were also significantly associated with timepoint 2 T2 relaxation times (r_s = 0.98 to r_s = 0.88 [P = .00003 to P = .004]) (*y-axis* of graph, Figure 5D). Additionally, baseline T2 relaxation times (*x-axis* of graph, Figure 5E, F) were highly correlated with changes in IPSG cartilage scores (r_s = 0.93 to r_s = 0.86 [P = .001 to P = .007]) (*y-axis* of graph, Figure 5E) and T2 relaxation times (r_s = 0.79 to r_s = 0.62 [P = .021 to P = .102]) (*y-axis* of graph, Figure 5F) in most ROIs.

4 | DISCUSSION

Our study showed a broad increase in T2 relaxation times across all study subjects, suggesting that age may contribute to altered values over time, consistent with other studies that have found T2 relaxation times to increase with age in asymptomatic adults [23], adults with patellar chondromalacia [24], and children with juvenile idiopathic arthritis [38]. Importantly, Persons with hemophilia showed greater increases in T2 relaxation times than healthy subjects, raising the possibility that elevated T2 relaxation times in persons with hemophilia resulted from a combination of age-associated cartilage changes and blood-induced cartilage degradation. This was further shown in the strong correlations seen between changes in T2 relaxation times and in IPSG cartilage scores over time, suggesting that the greater increase in T2 relaxation times seen in the hemophilic group than in the control

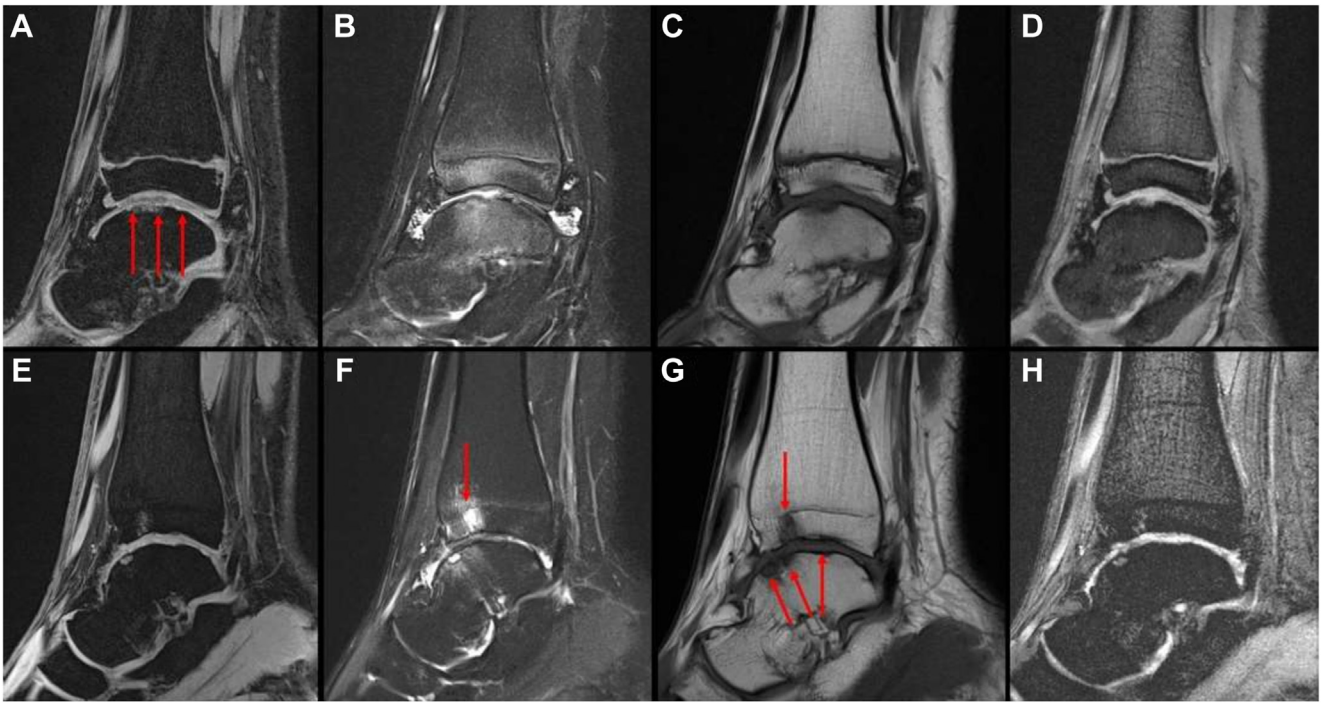

FIGURE 4 Example of interval progression of existing conventional MRI-detectable cartilage damage at timepoint 1. Sagittal T1 volumetric interpolated breath-hold examination and corresponding sagittal SPectral Attenuated Inversion Recovery (STAIR) T2, T2 map (echo times of 9.6/19.2/28.8 ms), gradient recalled MR images of the left ankle of a boy with hemophilia with ages of 12 and 17 years old at timepoints 1 (A–D) and 2 (E–H). At timepoint 1, structural bone erosions involved >50% of the articular surface of the proximal talus (arrows, score 2, A) and partial loss of the articular cartilage of the proximal talus was noted over >50% of the articular surface (score 2) with minimal cartilage loss of the distal tibia. No subchondral cysts were identified by the tibiotalar joint. At timepoint 2 more extensive structural cartilage changes were noted involving >50% of the articular surface of both distal tibia and talar dome with focal full-thickness cartilage loss (not shown) (score 3). Bone erosions also progressed horizontally along the articular surface in the interval but score 2 persisted as it already represented the maximum score for this abnormality (ceiling effect). Subchondral cyst formation developed on both sides of the joint anteriorly (arrows, score 2, F, G). Mild soft tissue changes were noted by the tibiotalar joint at both timepoints. Cartilage International Prophylaxis Study Group (IPSG) MRI scores at the tibiotalar joint for timepoints 1 and 2 were 2 and 3, respectively, whereas weight bearing cartilage T2 relaxation times at the tibiotalar joint for timepoints 1 and 2 were 62.8 and 98.2 ms, respectively.

group could relate to the sensitivity of T2 relaxation times to arthropathic cartilage changes over time in hemophilia. Although this sensitivity to change of T2 mapping has been proposed in several previous cross-sectional studies of persons with hemophilia [21] and with other disease-derived arthropathies [26,27], and longitudinally in patients with osteoarthritis [31], to our knowledge, this is the first longitudinal study in persons with hemophilia and arthropathy to document this observation in a small series. Note should be made, however, that an increase in T2 relaxation time occurred both in persons with hemophilia and in age- and sex-matched healthy controls over time likely reflecting a combined effect of physiologic cartilage T2 mapping and degradational cartilage changes over time in patients with hemophilia, which is difficult to be assessed by statistical parameters only.

T2 mapping also demonstrated prognostic value in detecting changes in cartilage prior to anatomic MR imaging detection. T2 relaxation times of initial examinations in persons with hemophilia were strongly predictive of second visit IPSG cartilage scores and changes in these scores over time in all joint regions. Further, persons with hemophilia with IPSG cartilage score progression had significantly longer baseline T2 relaxation times in weight bearing regions than the control group, suggesting a prognostic value of T2 mapping. This may have occurred only in weight bearing regions as early signs of cartilage degradation are thought to initiate in the weight bearing regions of the articular cartilage, consistent with previous studies showing increased T2 relaxation times in weight bearing regions [21]. Importantly, the majority of patients showing clinical progression of cartilage degradation demonstrated no anatomic MRI-visible cartilage damage at their first examination, suggesting that T2 mapping can detect early cartilage changes that are not seen on conventional MRI. Overall, these results point of the possibility that baseline T2 relaxation times indicate an increased likelihood of bleed-related cartilage degradation and the need to consider changes in management strategy targeted at compliance with the prescribed prophylaxis regimen in noncompliant subjects or intensification in the prophylaxis regimen in subjects judged to be compliant.

Previous investigations have suggested a biochemical rationale to support the concept that differences in T2 relaxation times reflect cartilage changes and can predict degradation. Owing to the orientational dependence of T2 relaxation times, cartilage with high anisotropy shows low T2 relaxation times compared with disorganized

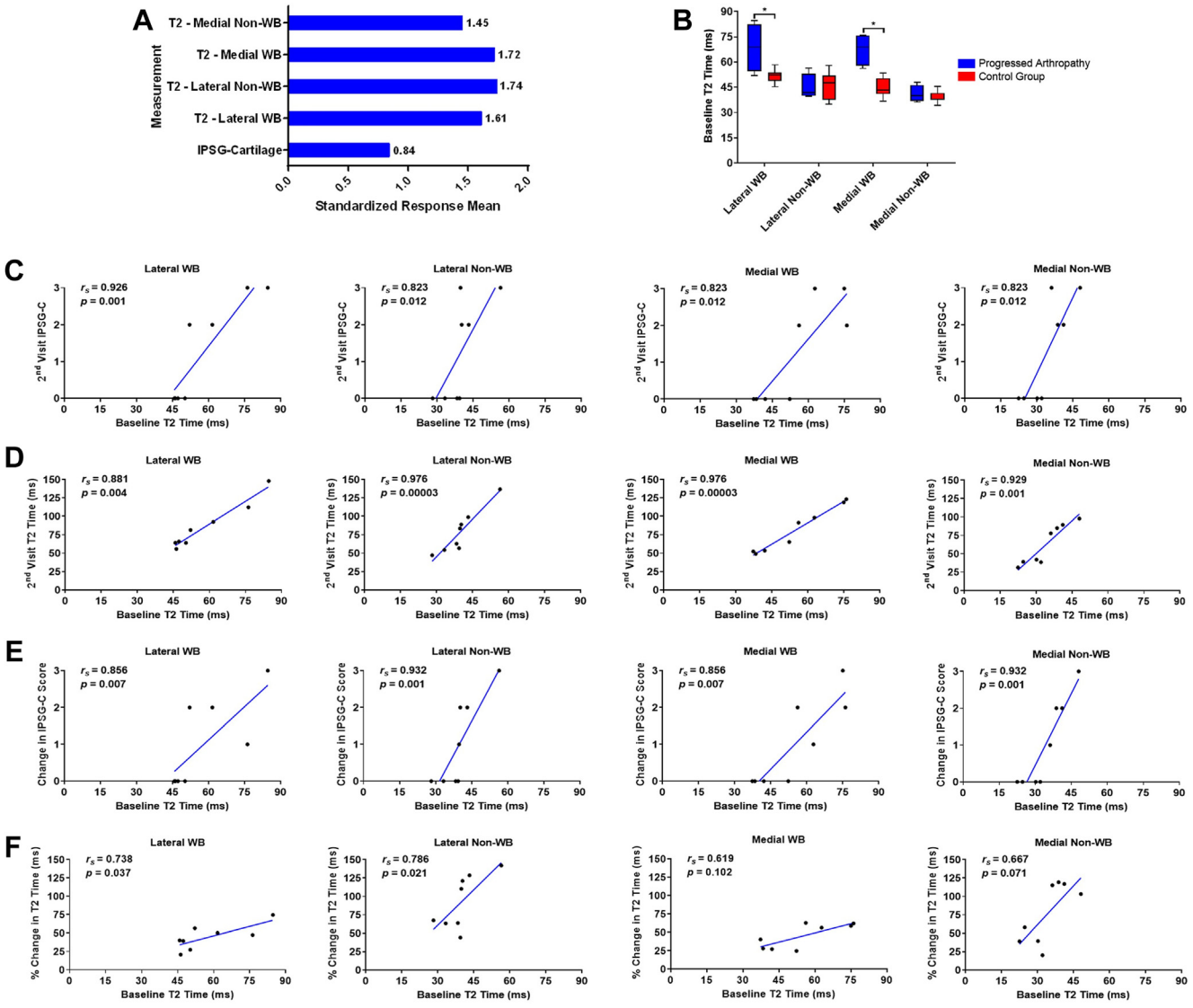

FIGURE 5 Responsiveness and predictive value of baseline T2 relaxation time for future cartilage damage. (A) Standardized response means of IPSG cartilage score and T2 relaxation time for all regions-of-interest. Standardized response mean (SRM) values of >0.8 represent large changes [30]. The SRM of T2 relaxation times in different regions of the ankle cartilage were all greater than 1.40, whereas the SRM of the IPSG structural cartilage magnetic resonance imaging (MRI) scores was 0.84, at the minimum range of the large changes' category of SRM. This shows a larger magnitude of SRM noted for T2 mapping values. (B) Baseline T2 relaxation times of study subjects with hemophilia who demonstrated progression of IPSG MRI cartilage scores over time (in blue) were greater than those of healthy controls (in red). A single asterisk indicates statistical significance at $P < .05$. (C) Correlations between baseline T2 relaxation times and IPSG structural MRI cartilage scores at timepoint 2 in persons with hemophilia. (D) Correlations between baseline T2 relaxation times and timepoint 2 T2 relaxation times in persons with hemophilia. (E) Correlations between baseline T2 relaxation times and change in IPSG cartilage scores over time in persons with hemophilia. (F) Correlations between baseline T2 relaxation times and change in T2 relaxation times over time in persons with hemophilia. IPSG, International Prophylaxis Study Group; WB, weight bearing.

cartilage [39]. Unhealthy joints experience collagen fatigue and breakdown, resulting in a loss of tensile strength from the collagen matrix. This leads to proteoglycan swelling and an increase in cartilage water content and mobility [40]. Disorganization of collagen fibrils is seen in aging [41] and is strongly correlated with predegradational activity in cartilage [42], which may explain the increase in T2 relaxation times and changes in these times of cartilage seen here in persons with hemophilia. Hence, changes in cartilage anisotropy and proteoglycan content are likely important in the quantitative T2 mapping assessment of arthropathy.

The current treatment for hemophilia in most resource abundant countries consists of long-term prophylaxis instituted at an early age in life for persons with hemophilia and a severe bleeding phenotype, which effectively but not completely prevents joint bleeds [10]. Current anatomic MRI acquisition protocols in persons with hemophilia detect macroscopic cartilage damage and are not sensitive to very

early microscopic changes in cartilage health. Macroscopic cartilage changes are thought to be irreversible [43], emphasizing the importance of early detection of bleed-related cartilage damage at a stage when changes can still be reversed to allow for more effective personalized treatment. The potential value of T2 mapping in persons with hemophilia and a severe bleeding phenotype is of particular importance in countries with reliable access to highly effective factor and nonfactor hemostatic agents for use in long-term prophylaxis introduced in boys with moderate or severe hemophilia from a very early age in life as recommended by the *World Federation of Hemophilia* [44]. In such boys, only minimal to mild bleed-related osteochondral changes are expected over time [9]. Identification of such changes at a very early stage in the evolution of hemophilic arthropathy through T2 mapping of the index joints (ankles, knees, and elbows) offers the potential for interventions targeted at limiting or preventing progressive cartilage damage. This imaging technique holds promise as a surveillance outcome measure tool to quantitate the rate of progression of cartilage damage or even the reversal of existing cartilage damage in persons with hemophilia presenting with a severe bleeding phenotype who are started on effective long-term prophylaxis or who undergo gene therapy. Thus, this imaging technique can improve the utilization of increasingly scarce resources in the healthcare system concerning hemophilia and other bleeding disorders.

Nevertheless, as shown in Table 2, the principle of inherent susceptibility of individuals to hemarthrosis may also play a role in the likelihood of development of hemophilic arthropathy. Whereas some joints with a large number of prior hemarthrosis at the time of the baseline MRI present with normal follow-up MRI scores, some joints with no clinically evident hemarthrosis at baseline may demonstrate the development of marked cartilage damage on the follow-up MRI, as previously reported [9]. It is possible that in addition to the inherent individual susceptibility to hemarthrosis, several other factors such as presence of iron/blood in the joint, limb posture, plantar longitudinal arch angle, joint alignment, and weight-bearing/non–weight-bearing role of the joint, conjointly contribute to future joint outcomes concerning cartilage degeneration.

This study has methodological limitations. Chief among them is the small sample size. Hence, the observations of this case series require confirmation of results in a future longitudinal prospective studies with larger numbers of subjects. However, the preliminary results of this case series are encouraging concerning the value of this noninvasive and readily available technique. This provides motivation for larger scale studies to further validate this technique. ROIs were selected and analyzed multiple times throughout multiple studies with consistent values, providing high confidence in the reproducibility of measurements by a single operator. These operators were trained using the methodology of a previous study, yielding high intrarater reliability (ICC = 0.92) and interrater reliability (ICC = 0.82) of measurements upon comparison of the same patients [22]. ROI placement and differences in MRI systems and parameters may account for any differences in T2 relaxation times relative to other previous studies. The non–weight-bearing regions often differed in size due to differences in cartilage availability, limiting the consistency of the study as it failed to provide a standardized length for these regions which may anatomically differ. Angular differences in slices imaged between different cases may have caused inconsistencies in cartilage availability. Another limitation is that the T2 mapping protocol in this study used 3 echoes. This may have limited our measurement precision, particularly due to the utilization in ankles joints which have thinner articular cartilages than other large joints such as knees. Future studies should employ further optimization of the T2 mapping protocol.

Although clinical IPSG scores were provided by a single experienced radiologist, this scoring system has been shown to be highly reproducible across musculoskeletal radiologists [45]. This study is a case series, rather than a preplanned prospective cohort study. Therefore, it did not control for variations in therapy over the course of the study and physical activity of the persons with hemophilia. Variations in physical activity may influence joint health, risk of joint bleeds, and subsequent cartilage damage [46]. As such further studies using T2 mapping prior, during, and after physical activity are needed. Moreover, all study subjects were from within Canada, and all received similar standard prophylaxis aimed at preventing spontaneous bleeding into joints and muscles. Further, the lack of participation of a substantial number of patients who had previously been scanned with T2 mapping MRI as adolescents in our institution [22] may have posed selection bias to the study.

A limitation regarding socioeconomic determinants relies on the fact that no race or ethnic background could be obtained from study patients as per local guidelines at the time of data collection which has implications on applicability of the study results to different ethnic populations in the country where the study was conducted and elsewhere in the world. Finally, the ultimate goal of prophylaxis in hemophilia is the maintenance of pristine joints. Considering that the study results suggest that T2 mapping MRI can be an early biomarker of joint damage in hemophilia, future studies could address how asymptomatic joints of persons with hemophilia, without a history of clinically evident joint bleeds, behave over time with respect to early cartilage degeneration by T2 mapping in comparison to structural MRI. Whereas such assessment would minimize confounding effects of optimization of prophylaxis to patients which is performed in the presence of clinically evident joint bleeds, it would pose challenges for serial MRI data acquisition from the 6 large joints most frequently involved in hemophilia, elbows, knees, and ankles [47], as one would not know which of them would develop future cartilage degeneration in the presence of prior subclinical bleeds. Also, note should be made that although this MRI technique can be particularly valuable to young children prior to irreversible damage to their joint cartilage, this is the population for which the utilization of MRI can be challenging due to the need for sedation or general anesthesia. Therefore, other early biomarkers of early cartilage damage in hemophilia and other musculoskeletal disorders should be pursued. Future clinical translation and broad utilization of the proposed MRI technique in younger patients will depend on development of MRI or artificial intelligence technologies for reduction of scan time [48,49], on implementation of distraction methods for MRI scanning, eg, virtual reality, dog suppport [50], and on the easiness of access and availability of MRI scanners across the globe [51].

5 | CONCLUSION

The results of this study suggest that T2 mapping MRI is a promising candidate technique to assess the status of articular cartilage in boys and adolescents with hemophilia. It has shown potential to detect changes in cartilage prior to macroscopic cartilage degradation evident using conventional anatomic MR imaging acquisition protocols, and could therefore act as a predictor for future cartilage progression. This is of particular importance in our current era of new therapies including gene therapy in the management of hemophilia and other joint-related bleeding disorders.

6 | CLINICAL PRACTICE APPLICATION

Concerning translation into clinical practice, further investigation of T2 mapping MRI in larger longitudinal series of persons with hemophilia and control subjects is needed to determine T2 relaxation time values' cutoffs and reasonable SD intervals for a given patient's age above which they can predict unfavorable future cartilage degeneration. At the present time most of the commercially available clinical MRI scanners offer built-in T2 mapping capabilities for data acquisition and analysis. As these technological advances become more accessible to the global population T2 mapping capabilities may become available as a routine clinical practice, if the results of this preliminary study demonstrating the clinical value of the technique are confirmed in larger series.

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AUTHOR CONTRIBUTIONS

This study was conceptualized and designed by A.D., B.B. Data were collected by T.R., R.W., and C.M. Data analysis and interpretation was performed by B.B., R.M., H.M., and A.D. The manuscript was drafted by B.B. and A.D. with input from all authors, and all authors revised and approved the final manuscript.

RELATIONSHIP DISCLOSURE

Dr A. Doria has had the following relationships unrelated to the conduct of this study: advisory boards of the International Myositis Assessment & Clinical Studies Group (not for profit) and the OMERACT SIG in MRI in JIA and OMERACT Technical Advisory Group (not for profit), and research support from Baxalta-Shire (Research Grant), Novo Nordisk (Research Grant), the Terry Fox Foundation (Research Grant), the PSI Foundation (Research Grant), the Society of Pediatric Radiology (Research Grant), and the Garron Family Cancer Centre (Research Grant).

Dr J. Teitel has had the following relationships unrelated to the conduct of this study: advisory boards for Novo Nordisk, Pfizer, Bayer, CSL Behring, and Takeda Pharmaceuticals, invited speaker for Pfizer, research support from Pfizer, Spark, Bayer, and Takeda Pharmaceuticals, and consulting for Regeneron, Pfizer, Bayer, and BioMarin.

Dr V. Blanchette has had the following relationships unrelated to the conduct of this study: consultancy and speaker fees from Amgen, Bayer, Bioverativ/Sanofi, Novo Nordisk, Pfizer, Roche, Shire/Takeda, and Spark Therapeutics. He is recipient of research grants from Bioverativ/Sanofi, Bayer, Novo Nordisk, and Shire, and serves as a member of Data Safety Monitoring Boards for Octapharma and Shire/Takeda. He is also the Chair of a nonprofit organization, the IPSG.

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