

UC San Diego

UC San Diego Previously Published Works

Title

Advanced magnetic resonance imaging of cartilage components in haemophilic joints reveals that cartilage hemosiderin correlates with joint deterioration

Permalink

<https://escholarship.org/uc/item/88m175h4>

Journal

Haemophilia, 25(5)

ISSN

1351-8216

Authors

von Drygalski, Annette
Barnes, Richard FW
Jang, Hyungseok
[et al.](#)

Publication Date

2019-09-01

DOI

10.1111/hae.13802

Peer reviewed

ORIGINAL ARTICLE

Musculoskeletal

Advanced magnetic resonance imaging of cartilage components in haemophilic joints reveals that cartilage hemosiderin correlates with joint deterioration

Annette von Drygalski^{1,2}  | Richard F. W. Barnes¹ | Hyungseok Jang³ | Yajun Ma³ | Jonathan H. Wong³ | Zachary Berman³ | Jiang Du³ | Eric Y. Chang^{3,4}

¹Department of Medicine, University of California San Diego, San Diego, California

²Department of Molecular Medicine, The Scripps Research Institute, La Jolla, California

³Department of Radiology, University of California San Diego, San Diego, California

⁴Radiology Service, VA San Diego Healthcare System, San Diego, California

Correspondence

Annette von Drygalski, Hemophilia and Thrombosis Treatment Center, University of California San Diego, 9333 Genesee Ave Suite 310, San Diego, CA 92121.
Email: avondrygalski@ucsd.edu

Funding information

This study is supported by Bioverativ (now Sanofi) (AvD), and by funding from the Health Resource and Service Agency (HRSA) H30MC24045. EYC acknowledges support from the Veterans Affairs Clinical Science and Rehabilitation Research and Development Services (I01CX001388 and I01RX002604).

Abstract

Introduction: Evidence suggests that toxic iron is involved in haemophilic joint destruction.

Aim: To determine whether joint iron deposition is linked to clinical and imaging outcomes in order to optimize management of haemophilic joint disease.

Methods: Adults with haemophilia A or haemophilia B ($n = 23$, \geq age 21) of all severities were recruited prospectively to undergo assessment with Hemophilia Joint Health Scores (HJHS), pain scores (visual analogue scale [VAS]) and magnetic resonance imaging (MRI) at 3T using conventional MRI protocols and 4-echo 3D-UTE-Cones sequences for one affected arthropathic joint. MRI was scored blinded by two musculoskeletal radiologists using the International Prophylaxis Study Group (IPSG) MRI scale. Additionally, UTE-T2* values of cartilage were quantified. Correlations between parameters were performed using Spearman rank correlation. Two patients subsequently underwent knee arthroplasty, which permitted linking of histological findings (including Perl's reaction) with MRI results.

Results: MRI scores did not correlate with pain scores or HJHS. Sixteen joints had sufficient cartilage for UTE-T2* analysis. T2* values for cartilage correlated inversely with HJHS ($r_s = -0.81$, $P < 0.001$) and MRI scores ($r_s = -0.52$, $P = 0.037$). This was unexpected since UTE-T2* values decrease with better joint status in patients with osteoarthritis, suggesting that iron was present and responsible for the effects. Histological analysis of cartilage confirmed iron deposition within chondrocytes, associated with low UTE-T2* values.

Conclusions: Iron accumulation can occur in cartilage (not only in synovium) and shows a clear association with joint health. Cartilage iron is a novel biomarker which, if quantifiable with innovative joint-specific MRI T2* sequences, may guide treatment optimization.

KEYWORDS

arthropathy, cartilage, haemophilia, hemophilia joint health score, hemosiderin, iron, magnetic resonance imaging

1 | INTRODUCTION

Arthropathy caused by frequent spontaneous joint bleeding is a progressive and debilitating co-morbidity in haemophilia.¹ The most salient features of haemophilic arthropathy are intra- and periarticular soft tissue inflammation with hypertrophy and osteochondral destruction.²⁻⁵ In addition to insufficient plasma clotting factor activity levels, vascular instability caused by neovascularization, vessel remodelling and abnormal vessel leakiness may fuel a vicious cycle of re-bleeding, thereby promoting arthropathic progression.^{3,6-8}

Supported by observations from explanted cartilage and haemophilia mouse and dog models, the concept has emerged that iron released from red cells and subsequently stored as hemosiderin in articular soft tissues creates a 'toxic' environment.⁹ As a consequence, dysregulation of joint tissue metabolism, synovial inflammation and hypertrophy occur, ultimately resulting in cartilage destruction.⁵ However, a more exact understanding of the influence of joint iron deposition on clinical outcomes and the progression of arthropathy in relation to imaging findings in patients with haemophilia (PWH) is lacking.

The purpose of this study was to evaluate joints of adult PWH using conventional and quantitative ultrashort time-to-echo (UTE) magnetic resonance imaging (MRI) sequences to delineate imaging pathology according to IPSG recommendations,¹⁰ which also assess hemosiderin content semi-quantitatively, and to determine whether findings correlate with Hemophilia Joint Health Scores (HJHSs) and pain. Ultimately, we felt that such knowledge would improve our clinical understanding of haemophilic arthropathy and help to optimize the use of clinical and radiological assessments for therapeutic management.

2 | MATERIALS AND METHODS

2.1 | Patient population and data extracted

Adult patients with haemophilia A or haemophilia B of all severities (denoted as severe, moderate or mild depending on intrinsic factor FVIII or IX plasma activity of <1%, 1%-5% or ≥5%, respectively), age 21 years and older (n = 23), and seen consecutively during routine clinic visits over a 4-month period, underwent MRI examination of one painful or uncomfortable joint. At inclusion, Hemophilia Joint Health Scores (version 2.1) of the affected joints¹¹ (HJHS, 0 best, 20 worst) were determined for the affected joint by a licensed physical therapist with >5 years of general practice experience and approximately 2 years of experience with haemophilia patients. The physical therapist was trained in the HJHS acquisition according to instructions and guidance provided by online training and video modules developed by the International Prophylaxis Study Group (<http://www.ipsg.ca/publication/hemophilia-joint-health-score-instructional-video-and-manual>). Pain was self-assessed by visual analogue scale (VAS; 0 no pain; 10 worst pain). In terms of patient demographics, only age, type and severity of haemophilia were extracted from the electronic medical record.

The study protocol, data acquisition and patient confidentiality safeguards were approved by the Human Research Protection Program (HRPP) at the University of California San Diego (UCSD), and patients provided written informed consent.

2.2 | MR imaging

MR imaging was performed on a clinical 3T scanner (Signa HDx, GE Healthcare Technologies) and either an 8-channel knee coil, 4-channel ankle coil or an 8-channel flexible surface coil (for knees, ankles and elbows, respectively) using the following 2D sequences: sagittal fast spin-echo (FSE) T1-weighted (650/10 ms; echo-train length of 4; 4 mm slice thickness; 0.5 mm interslice gap; 384 × 320 matrix; 14 cm field of view; and 1 signal average), sagittal FSE T2-weighted with fat suppression (4000/65 ms; echo-train length of 12; 4 mm slice thickness; 0.3 mm interslice gap; 384 × 288 matrix; 14 cm field of view; and 2 signal averages), coronal FSE T1-weighted (650/10 ms; echo-train length of 4; 4-mm slice thickness, 0.5-mm interslice gap, 384 × 320 matrix, 14-cm field of view, and 2 signal averages), coronal FSE T2-weighted with fat suppression (5000/65 ms, echo-train length of 16, 4-mm slice thickness, 0.5-mm interslice gap, 384 × 320 matrix, 14-cm field of view, and 1 signal average), axial FSE T1-weighted (650/10 ms; echo-train length of 4; 4-mm slice thickness; 0.5-mm interslice gap; 320 × 288 matrix; 14-cm field of view; and 1 signal average) and axial FSE intermediate-weighted with fat suppression (3200/40 ms; echo-train length of 9; 4-mm slice thickness; 0.5-mm interslice gap; 320 × 288 matrix; 14-cm field of view; and 1 signal average). In addition, sagittal three-dimensional (3D) ultrashort echo time (UTE) images were acquired with a cones readout trajectory at four different echo times (TR/TEs, 15 ms/0.03, 2.8-3, 5.6-6 and 8.4-9 ms; flip angle = 11°; 4 mm slice thickness; 256 × 256 matrix, 14-cm field of view, time ~6 minutes).¹² Intravenous contrast was administered for select cases when clinically indicated.

2.3 | Image interpretation and data analysis

The International Prophylaxis Study Group (IPSG) MRI score¹⁰ was applied by a fellowship-trained, musculoskeletal radiologist with 6 years of experience and a fourth-year radiology resident. Both were blinded to each other's scores as well as clinical scores. The soft tissue domain, composed of effusion/hemarthrosis, synovial hypertrophy and hemosiderin, has a maximum score of 9. The osteochondral domain, composed of surface erosions, subchondral cysts and cartilage degradation, has a maximum score of 8. The IPSG MRI score has a maximum combined score of 17. The presence and extent of hemosiderin deposition were determined by evaluating the multi-echo UTE sequence, with special consideration to avoid misinterpreting as hemosiderin chemical shift artefacts of the second kind for voxels containing both fat and water on out-of-phase TEs.¹³

Using the sagittal multi-echo UTE images, a slice extending through the centre of each articulation was selected, and regions of interest (ROIs) were carefully placed on the midportion of the

patellar and talar cartilage (weight-bearing articulations) on the selected slice. Most elbows exhibited severe osteochondral wear with little or no cartilage left for quantitative MRI analysis and therefore were excluded from further analyses. ROIs were selected to minimize volume averaging artefacts. T2* values were calculated using a Levenberg-Marquardt fitting algorithm developed in-house in MATLAB (The Mathworks Inc).

2.4 | Human joint tissue and histology

The harvesting of human tissues at the time of total knee replacement surgery was approved by the UCSD HRPP. To assess cartilage changes and iron deposition by histopathology, bone pieces containing articular cartilage were sawed into approximately 2 × 1 cm pieces and fixed in formalin for >1 week. Pieces were rinsed and demineralized by daily changes of 10% formic acid in the presence of 0.2% potassium ferrocyanide to achieve en bloc Perls' reaction before loss of ferric ions in the acid demineralization solution. Decalcification included 5 days of formic acid, followed by 5 days of saline rinsing. Pieces of decalcified Perls'-reacted tissue were cryoprotected in 30% sucrose and cryosectioned at 8 μm before counterstaining with haematoxylin or periodic acid-Schiff stain. To limit staining to only light red nuclei with haematoxylin, modified Harris haematoxylin (SH30, Fisher Scientific) was mixed 1:2 with 0.5% aqueous acetic acid and applied for only 1 minute before differentiation in 70% ethanol with 1% HCl.

2.5 | Statistical analysis

Descriptive statistics were used to describe the patient cohort. Correlations between cartilage (T2*) MRI findings with pain, HJHS and MRI IPSPG score were achieved by Spearman rank test. The consistency between the two radiologists was evaluated with the intraclass correlation coefficient.¹³

3 | RESULTS

3.1 | Patient and joint characteristics

The cohort characteristics are summarized in Table 1. Briefly, 23 patients (median age 42 years, standard deviation [SDE] 15 years) were recruited (seven ankles, nine knees, seven elbows) and imaged with MRI. There were 18 patients with haemophilia A and 5 with haemophilia B. Only four patients had mild or moderate haemophilia; the other 19 patients had severe haemophilia. MRI scores were very similar between the two readers and were averaged. There was a high degree of agreement: 0.95 and 0.98 for soft tissue total and osseous total, respectively.

Mean HJHS, VAS pain score and MRI IPSPG score were 5.5 (SDE 3.4, range 0-11), 3.0 (SDE 2.4, range 0-7) and 10.3 (SDE 3.9, range 0-16). When the IPSPG MRI score was divided into soft tissue and osteochondral domains, the mean scores were 3.2 (SDE 2.0, range 0-8) and 7.0 (SDE 2.4, range 0-8), respectively.

TABLE 1 Patient and joint characteristics

Characteristic	
Patient (n)	23
Haemophilia A	18
Haemophilia B	5
Severity (n)	
Mild/Moderate	4
Severe	19
Age (y; mean [SDE])	41.6 (15.2)
Joints (n)	
Knee	9
Elbow	7
Ankle	7
HJHS (mean [SDE])	5.5 (3.4)
Pain (VAS score; mean [SDE])	3.4 (2.8)
MRI IPSPG Score (mean [SDE])	10.3 (3.9)
Soft tissue domain	3.2 (1.9)
Osteochondral domain	Mode ^a = 8

Abbreviations: HJHS, Hemophilia Joint Health Score; IPSPG, International Prophylaxis Study Group; MRI, magnetic resonance imaging; SDE, standard deviation; VAS, visual analogue scale.

^aThis variable cannot be expressed as mean with SDE because of its distribution with a mode of 8 and a range from 0 to 8.5 (17 subjects have the same value of 8).

3.2 | Relationships between IPSPG MRI scores, pain and HJHS

There were no significant correlations between VAS pain scores and HJHSs with the MRI IPSPG scores, either total or divided into soft tissue or osteochondral sub-scores. Charting of data correlations revealed that advanced MRI findings, represented as total IPSPG score, or subdivided into the osteochondral and soft tissue domains, could be present at low HJHSs already, or even at a HJHS of zero. However, most abnormal MRI scores appeared above a HJHS of 3 (Figure 1).

3.3 | Quantification of iron in cartilage by MRI T2* relaxation and the relation to HJHS

Most elbows exhibited severe osteochondral wear with little or no cartilage left for quantitative MRI analysis. Therefore, iron quantification in cartilage was only performed on weight-bearing joints (knee and ankles, n = 16) and revealed a wide distribution of T2* values, with a mean T2* relaxation time of 9.2 ms (range 3.0-14.6 ms) (Figure 2A). Strong inverse correlations of T2* relaxation times with HJHSs ($r_s = -0.81$, $P < 0.001$) and IPSPG MRI scores ($r_s = -0.52$, $P = 0.037$) were noted (Figure 2 B/C), suggesting that iron was present in cartilage and that iron loading was associated with a higher degree of clinical and imaging-based arthropathic joint changes. When subdivided into osteochondral and soft tissue domains, the

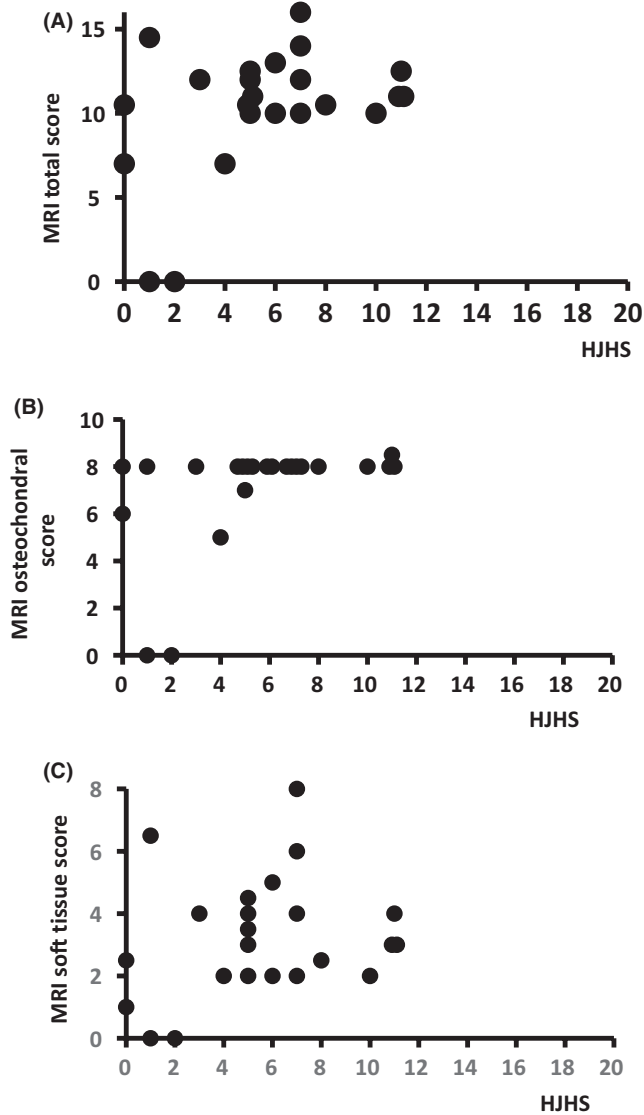


FIGURE 1 Relationship of HJHS and IPSG MRI scores. A, Total, B, osteochondral and C, soft tissue IPSG MRI scores were plotted against HJHS. HJHS, Hemophilia Joint Health Score; IPSG, International Prothylaxis Study Group; MRI, magnetic resonance imaging

MRI soft tissue score also correlated negatively ($r_s = -0.46$, $P = 0.076$) with T_2^* relaxation times. Correlation of the osteochondral MRI sub-score with T_2^* could not be performed on its own due to ceiling

effects of the MRI score, whereby 10 of 16 MRIs yielded the highest score of 8. Two examples, depicting iron quantification in the knee joint of a patient with severe haemophilia A and another patient with mild haemophilia A, are shown in Figure 3.

3.4 | Histological analysis of explanted cartilage for iron loading

To prove iron accumulation in cartilage as suggested by MRI, we examined cartilage explants, harvested subsequently (within 2 years) from two of the patients undergoing total knee replacement surgery. The corresponding T_2^* relaxation times in the patellae were 4.1 and 4.7 ms, which were among the lowest measured, indicating high iron loading. Perls' reaction revealed substantial iron deposits within the cartilage, mostly within and around chondrocytes, but also in lacunae-like structures lacking any apparent active cell. Representative examples of one patient are provided in Figure 4.

4 | DISCUSSION AND CONCLUSION

Quantitative MRI has been widely implemented for non-invasive evaluation of hyaline articular cartilage.¹⁴ Several studies have shown that chondral T_2 and T_2^* relaxation times are sensitive to water content, collagen content and collagen fibril orientation.¹⁵⁻¹⁷ Classically, elevated T_2 values in cartilage have been considered to represent irreversible damage to the extracellular matrix.¹⁸ Most recently, investigators have demonstrated that T_2^* , as measured by a multi-echo UTE technique similar to that used in this study, was significantly elevated in cartilage of injured knees compared with uninjured controls.^{19,20} Based on these results from studies in non-haemophilic populations with injury or osteoarthritis, we expected to find a positive correlation between increasing T_2^* relaxation times and worsening joint status. However, we found a strong negative correlation between joint status determined by HJHS and MRI IPSG scores with relaxation times. This seemingly contradictory and surprising result may be explained by our histology results showing iron accumulation in the cartilage, which would decrease T_2^* .²¹ The strong negative correlation suggests that the T_2^* shortening is a result of severe chondral iron deposition dominating the effects.

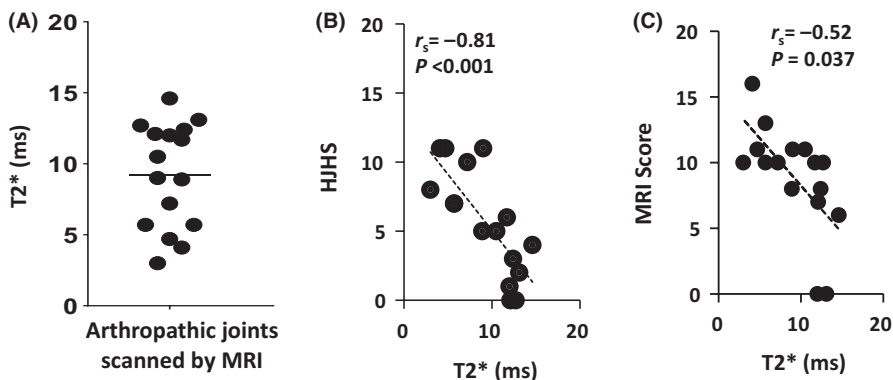


FIGURE 2 Quantification of iron in cartilage by MRI T_2^* relaxation in relation to HJHS and MRI scores. A, MRI T_2^* relaxation times were obtained from weight-bearing joints (knees and ankles, $n = 16$), and B, correlated with HJHSs and C, IPSG MRI scores by Spearman rank test. HJHS, Hemophilia Joint Health Score; IPSG, International Prothylaxis Study Group; MRI, magnetic resonance imaging; r_s , Spearman rank correlation coefficient

FIGURE 3 Magnetic resonance imaging quantification of iron in cartilage by T2*. Representative examples of A, high cartilage iron content ($T2^* = 3$) in the knee of a patient with severe haemophilia A (HJHS 8; MRI IPGS score 10) and B, low cartilage iron content ($T2^* = 12.1$) in the knee of a patient with mild haemophilia A (HJHS 1; MRI IPGS score 7). Left images demonstrate sagittal multi-echo UTE images with regions of interest drawn in the midportion of the patella. Right images demonstrate excellent curve fitting. HJHS, Hemophilia Joint Health Score; IPGS, International Prophylaxis Study Group; MRI, magnetic resonance imaging [Colour figure can be viewed at wileyonlinelibrary.com]

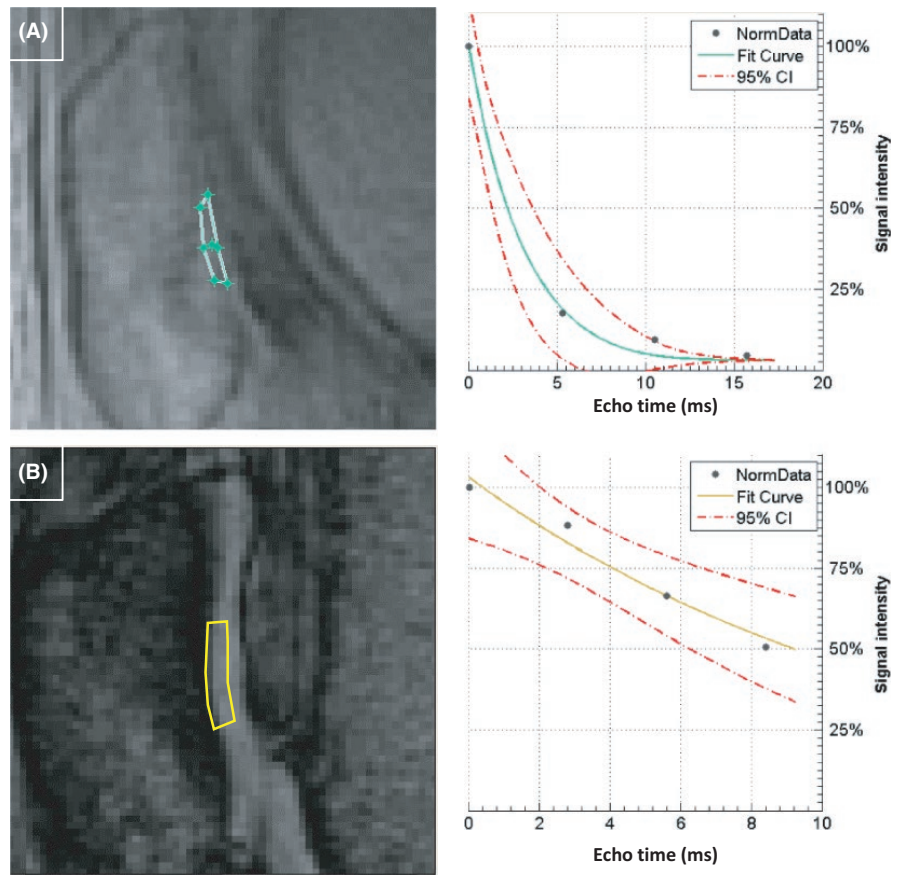
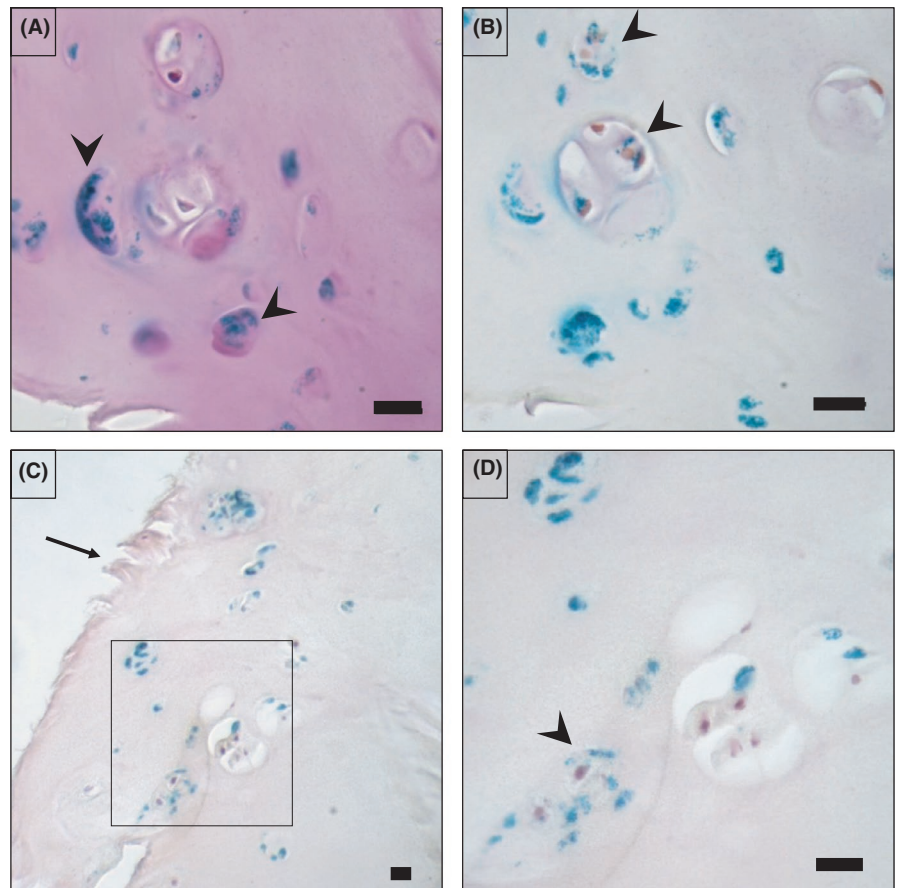


FIGURE 4 Histological depiction of iron accumulation in cartilage. Knee cartilage explants from a patient with haemophilia and osteoarthritis were examined histologically with Perls' reaction for iron content. A, Shows an iron-rich region counterstained with PAS, showing association of iron with chondron borders (25× objective). B, Same area counterstained for nuclei only with red haematoxylin on nearby section. C, Another area of wide iron distribution with red haematoxylin counterstain for nuclei (10× objective), with boxed region shown in D (25× objective). Fibrillation (arrow) and a paucity of chondrocytes are noted with many iron deposits (blue Perls' reaction product) in and around chondrocytes (example areas are denoted by arrow head). Bars 20 μm [Colour figure can be viewed at wileyonlinelibrary.com]



Iron deposition in chondrocytes of deteriorating cartilage in humans was described decades ago in several case series of patients with hemochromatosis.²²⁻²⁴ However, not all studies analysing arthritic joints of patients with hemochromatosis have identified iron in cartilage while synovial iron was readily detectable.^{23,25,26} It has been suggested that the paucity of observations of iron in cartilage may be due to the lack of sensitivity of osteochondral iron to usual iron stains (such as Prussian blue/Perls' stain) in histological examinations, since iron particles are small (0.25-0.5 μ) and may be beyond microscopic resolution, or to the loss of iron due to acidic fixation and decalcification techniques of joint tissue.²² This has been elucidated by Ghadially et al²² where iron detection with light microscopy after Prussian Blue/Perls' staining was compared to electron probe X-ray analysis of articular cartilage of rabbits after induced chronic hemarthrosis. In keeping with this observation, abundant synovial hemosiderin has been reported in haemophilic joints, whereas cartilage iron deposition has only been described in one case by light microscopy.^{27,28} To our knowledge, there is only one additional case report, describing iron accumulation in cartilage in association with chronic hemarthrosis, but without an evident cause such as haemophilia.²⁹ Taken together, it appears that iron can accumulate in cartilage with or without hemarthrosis, but little to nothing is known about the mechanistic and molecular processes of cartilage iron loading, or its clinical consequences.

In hemochromatosis, it has been proposed that iron might contribute to the degeneration of cartilage, but a direct relationship between joint iron accumulation and degree of arthritis has not been established.^{28,30,31}

To date, there is no knowledge about the extent of iron accumulation in cartilage of haemophilic joints in relation to joint status, function or dynamics of joint deterioration.

Somewhat surprisingly, observations from this study demonstrated that there was *no* correlation between clinical (HJHS) and imaging (MRI) scores, with highly abnormal imaging findings present over a wide spectrum of clinical scores. Similarly, widely divergent and mostly poor correlations between MRI IPSPG scores and HJHS were reported previously,³²⁻³⁴ especially in relation to the soft tissue compartments,³² possibly dependent on joint type and articulations involved.³⁴ These findings suggest that, while depicting joint deterioration, imaging abnormalities may have limited bearing on clinical joint status, which may be driven at least in part by individual pain perception and functional mobility. In aggregate, these observations corroborate that the severity of imaging findings can be dissociated from clinical/functional joint status as has been observed in other arthritic conditions.³⁵ However, when imaging was focused on chemical iron quantification using T2* relaxation, significant correlations between iron content and clinical scores as well as imaging scores became evident. Reasons are unclear, but also indicate that both are affected proportionally by cartilage iron loading. These findings suggest that (a) iron accumulation in association with joint bleeding occurs in cartilage and not solely in synovial tissue as previously believed and (b) that iron, once deposited in cartilage, may play an important role for direct and continued cartilage toxicity,

destruction and the progression of haemophilic arthropathy. This is of importance since osteochondral changes in haemophilia are believed to be mediated more indirectly by the pro-inflammatory milieu created by iron in synovial fluid and the synovium^{5,36} rather than by direct deposition of iron in cartilage. In that sense, the pathways of iron uptake into cartilage and iron retention, potentially causing damage from 'inside-out' rather than from 'outside-in', as well as the potential for reversibility of cartilage iron loading are unknown.

These findings suggest a need not only to study molecular pathways of cartilage iron loading and retention, but also to develop and validate sensitive MRI iron quantification methodologies specific to cartilage or other joint tissues for more immediate clinical application. A number of novel quantitative MRI techniques are in development^{37,38} which, if adjusted for cartilage imaging, may provide sensitive methods to precisely quantify cumulative joint iron loading over time. Quantitative iron imaging would revolutionize the ability to recognize the consequences of subclinical bleeding and/or suboptimal treatment strategies in haemophilia. At present, hemosiderin quantification is only possible in a semi-quantitative fashion,^{10,32} which lacks sensitivity for dynamic, incremental measurements.

MRI T2* has been performed previously to quantify iron loading of solid organs (liver and heart) in iron overload disorders such as hemochromatosis, hemoglobinopathies or other conditions of transfusion iron overload,^{39,40} but has not been validated yet for iron loading of joint tissues. While our results strongly suggest that T2* imaging can detect cartilage iron, sequences will have to be adjusted, improved and validated for joints. The development of such appropriate T2* joint imaging sequences may come timely since the management of haemophilia is currently undergoing a paradigm shift. Traditionally, the reduction of symptomatic joint bleeding, often expressed as annual bleeding rate (ABR), has been the most important outcome parameter for clotting factor therapies. However, ABR may be insufficient to guide management decisions for (a) emerging non-factor therapies, such as the recently FDA-approved FVIII-mimetic emicizumab (Hemlibra[®], Genentech) improving coagulation profiles and (b) gene therapies on the horizon with anticipated constant elevation of plasma factor activity levels.⁴¹ Since these new therapies mitigate or abrogate the fluctuations between plasma peak and trough clotting factor activity levels, correction of subclinical bleeding (rather than overt clinical bleeding) and appropriate iron clearance from the joint is important. It is in this arena that hemosiderin quantitation in joints could become a valuable assessment tool to measure treatment success. In that sense, interval detection of accumulation of hemosiderin during long-term treatment plans, employing non-factor or clotting factor strategies, would indicate that the prescribed therapy may not be adequate. Optimization of therapy may be achieved by discussing improved compliance, switching strategies, and/or adjustments with respect to dosing and/or frequency of drug administration.

In summary, it appears important to recognize that hemosiderin accumulation occurs not only in synovium, but also in cartilage, a fact that may be generally underappreciated in haemophilia care due to difficult histological detection by conventional iron staining

methods. Since findings from our study revealed that the amount of cartilage iron is associated with deteriorating clinical and imaging joint status, we hypothesize that cartilage iron plays a significant role in the progression of haemophilic arthropathy. Therefore, cartilage iron could be considered a biomarker of joint health that may become directly quantifiable with innovative joint-specific MRI T2* sequences, thus guiding the adjustment of therapeutic strategies to optimize joint health in patients with haemophilia.

ACKNOWLEDGEMENTS

We thank Lena Volland, DPT, for performance of HJHSs. AvD has received consulting fees and speaker honoraria from Bioerativ.

DISCLOSURES

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

AUTHOR CONTRIBUTIONS

AvD and EYC designed the study and shared responsibilities for study oversight, coordination, data analysis and manuscript writing. RFWB performed all statistical analyses. EYC and ZTB performed MRI scoring. HJ, YM and JD performed MRI data analysis. JHW performed the histology and histological analysis. All authors critically reviewed the manuscript and approved it in its final version.

ORCID

Annette von Drygalski  <https://orcid.org/0000-0002-9426-6322>

REFERENCES

- Luck JV, Silva M, Rodriguez-Merchan CE, Ghaleb N, Zahiri CA, Finn RS. Hemophilic arthropathy. *J Am Acad Orthop Surg*. 2004;12:234-245.
- Acharya SS, Schloss R, Dyke JP, et al. Power Doppler sonography in the diagnosis of hemophilic synovitis—a promising tool. *J Thromb Haemost*. 2008;6:2055-2061.
- Bhat V, Olmer M, Joshi S, et al. Vascular remodeling underlies rebleeding in hemophilic arthropathy. *Am J Hematol*. 2015;90:1027-1035.
- Sun J, Hua B, Livingston EW, et al. Abnormal joint and bone wound healing in hemophilia mice is improved by extending factor IX activity after hemarthrosis. *Blood*. 2017;129:2161-2171.
- Wyseure T, Mosnier LO, von Drygalski A. Advances and challenges in hemophilic arthropathy. *Semin Hematol*. 2016;53:10-19.
- Kidder W, Chang EY, Moran C, Rose SC, von Drygalski A. Persistent vascular remodeling and leakiness are important components of the pathobiology of re-bleeding in hemophilic joints: two informative cases. *Microcirculation*. 2016;23:373-378.
- Kidder W, Nguyen S, Larios J, Bergstrom J, Ceponis A, von Drygalski A. Point-of-care musculoskeletal ultrasound is critical for the diagnosis of hemarthroses, inflammation and soft tissue abnormalities in adult patients with painful haemophilic arthropathy. *Haemophilia*. 2015;21:530-537.
- Cooke E, Zhou J, Wyseure T, et al. Vascular permeability and remodelling coincide with inflammatory and reparative processes after joint bleeding in factor VIII-deficient mice. *Thromb Haemost*. 2018;118:1036-1047.
- van Vulpen L, Holstein K, Martinoli C. Joint disease in haemophilia: pathophysiology, pain and imaging. *Haemophilia*. 2018;24(Suppl 6):44-49.
- 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.
- Hilliard P, Funk S, Zourikian N, et al. Hemophilia joint health score reliability study. *Haemophilia*. 2006;12:518-525.
- Chang EY, Du J, Chung CB. UTE imaging in the musculoskeletal system. *J Magn Reson Imaging*. 2015;41:870-883.
- Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull*. 1979;86:420-428.
- Chang EY, Ma Y, Du J. MR Parametric mapping as a biomarker of early joint degeneration. *Sports Health*. 2016;8:405-411.
- Liess C, Lüsse S, Karger N, Heller M, Glüer C-C. Detection of changes in cartilage water content using MRI T2-mapping in vivo. *Osteoarthritis Cartilage*. 2002;10:907-913.
- Menezes NM, Gray ML, Hartke JR, et al. T2 and T1rho MRI in articular cartilage systems. *Magn Reson Med*. 2004;51:503-509.
- Mlynárik V, Szomolányi P, Toffanin R, Vittur F, Trattinig S. Transverse relaxation mechanisms in articular cartilage. *J Magn Reson*. 2004;169:300-307.
- Mosher TJ, Dardzinski BJ. Cartilage MRI T2 relaxation time mapping: overview and applications. *Semin Musculoskelet Radiol*. 2004;8:355-368.
- Chu CR, Williams AA, West RV, et al. Quantitative magnetic resonance imaging UTE-T2* mapping of cartilage and meniscus healing after anatomic anterior cruciate ligament reconstruction. *Am J Sports Med*. 2014;42:1847-1856.
- Williams AA, Titchenal MR, Do BH, Guha A, Chu CR. MRI UTE-T2* shows high incidence of cartilage subsurface matrix changes 2 years after ACL reconstruction. *J Orthop Res*. 2018;37(2):370-377.
- Hong W, He Q, Fan S, et al. Imaging and quantification of iron-oxide nanoparticles (IONP) using MP-RAGE and UTE based sequences. *Magn Reson Med*. 2017;78:226-232.
- Ghadially FN, Oryschak AF, Ailsby RL, Mehta PN. Electron probe x-ray analysis of siderosomes in haemarthrotic articular cartilage. *Virchows Arch B Cell Pathol*. 1974;16:43-49.
- Schumacher HR. Articular cartilage in the degenerative arthropathy of hemochromatosis. *Arthritis Rheum*. 1982;25:1460-1468.
- Axford JS, Revell P, Watt I, Bomford A, Williams R, Hamilton E. Hip arthropathy in genetic hemochromatosis. Radiographic and histologic features. *Arthritis Rheum*. 1991;34:357-361.
- Atkins CJ, McIvor J, Smith PM, et al. Chondrocalcinosis and arthropathy: studies in haemochromatosis and in idiopathic chondrocalcinosis. *Q J Med*. 1970;39:71-82.
- Heiland GR, Aigner E, Dallos T, et al. Synovial immunopathology in haemochromatosis arthropathy. *Ann Rheum Dis*. 2010;69:1214-1219.
- Roosendaal G, van Rinsum AC, Vianen ME, van den Berg HM, Lafeber FP, Bijlsma JW. Haemophilic arthropathy resembles degenerative rather than inflammatory joint disease. *Histopathology*. 1999;34:144-153.
- van Vulpen L, Roosendaal G, van Asbeck BS, Mastbergen SC, Lafeber F, Schutgens R. The detrimental effects of iron on the joint: a comparison between haemochromatosis and haemophilia. *J Clin Pathol*. 2015;68:592-600.
- Matsumoto K, Ishimaru D, Ogawa H, Akiyama H. Black colouration of the knee articular cartilage after spontaneously recurrent hemarthrosis. *Case Rep Orthop*. 2016;2016:1238392.



30. Inês LS, da Silva JA, Malcata AB, et al. Arthropathy of genetic hemochromatosis: a major and distinctive manifestation of the disease. *Clin Exp Rheumatol*. 2001;19:98-102.
31. Vaiopoulos G, Papanikolaou G, Politou M, Jibreel I, Sakellaropoulos N, Loukopoulos D. Arthropathy in juvenile hemochromatosis. *Arthritis Rheum*. 2003;48:227-230.
32. Doria AS, Keshava SN, Mohanta A, et al. Diagnostic accuracy of ultrasound for assessment of hemophilic arthropathy: MRI correlation. *AJR Am J Roentgenol*. 2015;204:W336-W347.
33. Den Uijl I, De Schepper A, Camerlinck M, Grobbee DE, Fischer K. Magnetic resonance imaging in teenagers and young adults with limited haemophilic arthropathy: baseline results from a prospective study. *Haemophilia*. 2011;17:926-930.
34. Brunel T, Lobet S, Deschamps K, et al. Reliability and clinical features associated with the IPSPG MRI tibiotalar and subtalar joint scores in children, adolescents and young adults with haemophilia. *Haemophilia*. 2018;24:141-148.
35. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. *BMC Musculoskelet Disord*. 2008;9:116.
36. Haxaire C, Hakobyan N, Pannellini T, et al. Blood-induced bone loss in murine hemophilic arthropathy is prevented by blocking the iRhom2/ADAM17/TNF-alpha pathway. *Blood*. 2018;132:1064-1074.
37. Jang H, Lu X, Carl M, et al. True phase quantitative susceptibility mapping using continuous single-point imaging: a feasibility study. *Magn Reson Med*. 2018;81(3):1907-1914.
38. Lu X, Ma Y, Chang EY, et al. Simultaneous quantitative susceptibility mapping (QSM) and R2* for high iron concentration quantification with 3D ultrashort echo time sequences: an echo dependence study. *Magn Reson Med*. 2018;79:2315-2322.
39. Hernando D, Levin YS, Sirlin CB, Reeder SB. Quantification of liver iron with MRI: state of the art and remaining challenges. *J Magn Reson Imaging*. 2014;40:1003-1021.
40. He T. Cardiovascular magnetic resonance T2* for tissue iron assessment in the heart. *Quant Imaging Med Surg*. 2014;4:407-412.
41. Mahlangu J, Cerquiera M, Srivastava A. Emerging therapies for haemophilia - global perspective. *Haemophilia*. 2018;24(Suppl 6):15-21.

How to cite this article: von Drygalski A, Barnes RFW, Jang H, et al. Advanced magnetic resonance imaging of cartilage components in haemophilic joints reveals that cartilage hemosiderin correlates with joint deterioration. *Haemophilia*. 2019;25:851-858. <https://doi.org/10.1111/hae.13802>