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COMMENTARY

The relevance of MRI findings in joints of persons with haemophilia: Insights from the last decade

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Most bleeding episodes in persons with haemophilia (PwH) occur in the large synovial joints (elbows, knees, and ankles). Recurrent joint bleeding eventually leads to irreversible haemophilic arthropathy, which causes pain, reduced functionality, and thus reduced quality of life. Prophylactic treatment prevents most bleeding episodes.[1] Even in the absence of clinically overt joint bleeding, long-term progression to arthropathy is observed. Subclinical bleeding and inflammation are therefore thought to contribute to the development of arthropathy.[2–4] Detection of these subclinical processes is becoming increasingly important in the prevention of arthropathy in PwH as overt spontaneous joint bleeding is almost completely avoided by prophylaxis with new (non-factor) replacement therapies.[5]

Magnetic resonance imaging (MRI) is considered the gold standard for evaluation of early blood-induced joint changes in PwH. In 2005, the International Prophylaxis Study Group (IPSG) published compatible scales for progressive and additive MRI assessment based on the Denver MRI score and the European MRI score.[6] These scores were combined in a comprehensive scoring scheme in 2012.[7] Based on an appraisal of the original IPSG MRI scale,[8] the score is now updated to the *IPSG MRI Scale version 2.0* by Lundin and colleagues.[9] To provide more insight on the clinical relevance of MRI findings, we provide an overview of research on the clinical relevance of MRI findings evaluated by *IPSG MRI Scale version 2.0*.

1 | MRI DETECTS PREVIOUS (SUBCLINICAL) BLEEDING

Since the 1980s, there have been suspicions that chronic microbleeding or subclinical bleeding into the joints can cause arthropathy.[10,11] Manco-Johnson et al. found further evidence for this hypothesis after observing haemosiderin deposits and other joint changes on MRI in joints without any history of prior bleeding in a prospective clinical trial.[2] Potentially, prophylaxis may reduce subclinical bleeding and joint deterioration. Worth noting, haemosiderin deposits in joints without a history of bleeds were observed in 26% of Canadian children with severe haemophilia treated with tailored primary prophylaxis,[12] in 14% of Dutch adults with non-severe haemophilia (94% treated on demand),[13] and in 16% of Dutch adolescents and adults with severe haemophilia on prophylaxis.[14] These observations implicate that subclinical bleeding occurs in non-severe haemophilia and is not fully prevented by prophylaxis in severe haemophilia.

The (longer-term) clinical consequences of the observed signs of previous subclinical bleeding are a topic of interest. Haemosiderin accumulates in the synovial membrane and a previous study observed that haemosiderin deposits were accompanied by synovial hypertrophy in 88% of joints.[15] In addition, synovial hypertrophy was a strong and independent predictor for 5-year joint bleeding (OR = 10.1).[15] Another study showed that the presence of synovial hypertrophy or

haemosiderin on interval MRIs was associated with new osteochondral MRI changes at follow-up (OR = 4.7 and 5.3 respectively).[16] These results emphasize the importance of monitoring joint status in PwH using imaging which may be used to guide treatment.

2 | MRI EVALUATION OF JOINT EFFUSIONS

The *IPSG MRI Scale version 2.0* includes the evaluation of joint effusion/hemarthrosis.[9] Evaluation of joint effusion may be relevant for PwH during an acute episode to evaluate the presence of a potential bleed and may be incorporated in MRI interpretation for clinical care. However, joint effusion is not haemophilia specific and is not associated with 5-year joint bleeding or progression of arthropathy on radiographs according to previous studies using the IPSG MRI criteria.[15,17] As a result, the incorporation of joint effusion dilutes the disease specificity for long-term outcome assessment of haemophilic arthropathy. Future outcome studies using the *IPSG MRI Scale version 2.0* may take this into account by performing additional analyses without incorporation of effusion in the soft tissue subscore, or the sum score (summation of soft tissue and osteochondral subscores).

The accuracy of conventional MRI protocols in differentiating between physiological joint fluid and minor bleeding has not been conclusively determined.[18,19] Recently, it was shown that MRI T1 and T2 relaxometry could quantitatively distinguish synovial fluid from haemorrhagic joint effusion in vitro. The lowest detectable blood concentrations were 5% using T2 mapping at 3 Tesla MRI and 10% using T1 mapping at 1.5 Tesla MRI.[20] In vivo evaluation of the T2-relaxometry method at 3 Tesla MRI showed good feasibility and reproducibility.[21] The T2-relaxometry method needs to be validated in patients with (suspected) joint bleeding to evaluate the performance in a clinical setting. After validation, these methods could be incorporated into MRI protocols to evaluate joint effusions non-invasively for evaluation of difficult clinical cases or research purposes.

3 | MRI EVALUATION OF OSTEOCHONDRAL ABNORMALITIES

The *IPSG MRI Scale version 2.0* evaluates the following osteochondral changes separately; bone erosions and/or subchondral endplate irregularities, subchondral cysts, and cartilage degradation.[9] The updated definitions aimed to overcome the methodological challenges in the evaluation of osteochondral changes. Whether the adjustments in the *IPSG MRI Scale version 2.0* would alter previous MRI scores using the original IPSG MRI scale remains to be evaluated. Nonetheless, it is important to specifically mention which version of the MRI score was used for the manuscript in preparation to allow for a reliable comparison of studies.

Osteochondral changes may also result from normal wear and tear and are may be unrelated to joint bleeding in PwH. In a systematic review and meta-analysis, 5397 asymptomatic uninjured knees of 4751 adults were evaluated. The pooled prevalence of asymptomatic cartilage defects was 11% for subjects < 40 years and 43% for subjects ≥40 years.[22] In PwH, self-reported joint bleeds were associated with new osteochondral changes on MRI during follow-up.[16] These may later on progress into more severe arthropathy as observed in another study that showed that osteochondral MRI abnormalities were strongly associated with the development of abnormalities on x-rays 5 years later.[15] These x-ray abnormalities are negatively associated with physical functioning.[23] Therefore, evaluation of early osteochondral changes using MRI is important in the outcome assessment of current factor replacement therapies and new non-replacement therapies.

4 | MRI FOR RESEARCH AND CLINICAL CARE

As discussed above, MRI provides a complete overview of the joint status in PwH. Evaluated items of the new *IPSG MRI Scale version 2.0* may be clinically relevant as well. In clinical practise, MRI is especially useful for problem solving in cases where x-rays and ultrasound could not provide sufficient detail or understanding of the clinical complaints. Although formal scoring of MRIs may be unnecessary for clinical practice, reporting on items of the IPSG MRI Scale is recommended. A simplified version the new *IPSG MRI Scale version 2.0* for clinical usage is under development by the IPSG's Imaging Expert Working Subgroup.[9]

In summary, accumulating evidence from the past decade shows the relevance and potential of MRI for the evaluation of haemophilic arthropathy. The new *IPSG MRI Scale version 2.0* facilitates standardized MRI scoring of haemophilic arthropathy in future outcome studies in PwH.

CONFLICT OF INTEREST STATEMENT

F.L. declares no conflicts of interest. W.F. received research grants from NovoNordisk and Pfizer, all paid to the institution, and performed consultancy activities for Pfizer. M.T. received research grants from Novo Nordisk and SOBI and performed consultancy activities for SOBI, all paid to the institution. K.F. has received speaker's fees from Bayer, Baxter/Shire, Sobi/Biogen, CSL Behring and Novo Nordisk; has performed consultancy for Bayer, Biogen, CSL Behring, Freeline, Novo Nordisk, Roche and Sobi; and has received research support from Bayer, Baxter/Shire, Novo Nordisk, Pfizer and Biogen, all fees were paid to the institution.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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REFERENCES

1. Berntorp E, Fischer K, Hart DP, et al. Haemophilia. *Nat Rev Dis Primers*. 2021;7(1):45.

2. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al.. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. *N Engl J Med*. 2007;357:535-544.
3. Den Uijl IEM, De Schepper AM, Camerlinck M, et al. Magnetic resonance imaging in teenagers and young adults with limited haemophilic arthropathy: baseline results from a prospective study. *Haemophilia*. 2011;17(6):926-930.
4. Nijdam A, Foppen W, de Kleijn P, et al. Discontinuing early prophylaxis in severe haemophilia leads to deterioration of joint status despite low bleeding rates. *Thromb Haemost*. 2016;115(5):931-938.
5. Callaghan MU, Negrier C, Paz-Priel I, et al. Long-term outcomes with emicizumab prophylaxis for hemophilia A with or without FVIII inhibitors from the HAVEN 1–4 studies. *Blood*. 2021;137:2231-2242.
6. Lundin B, Babyn P, Doria a S, et al. Compatible scales for progressive and additive MRI assessments of haemophilic arthropathy. *Haemophilia*. 2005;11(2):109-115.
7. 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(6):962-970.
8. Tolend M, Majeed H, Soliman M, et al. Critical appraisal of the International Prophylaxis Study Group magnetic resonance image scale for evaluating haemophilic arthropathy. *Haemophilia*. 2020:26:565-574.
9. Lundin B, Bakeer N, Dunn AL, et al. International Prophylaxis Study Group (IPSG) haemophilia joint MRI scale version 2.0. *Haemophilia*. 2024;30:862-864. doi:10.1111/hae.15010
10. Pettersson H, Nilsson IM, Hedner U, Noréhn K, Ahlberg A. Radiologic evaluation of prophylaxis in severe haemophilia. *Acta Paediatr Scnd*. 1981;70:565-570.
11. Soreff J, Blomback M. Arthropathy in children with severe hemophilia A. *Acta Paediatr Scand*. 1980;69:667-673.
12. Kraft J, Blanchette V, Babyn P, et al. Magnetic resonance imaging and joint outcomes in boys with severe hemophilia A treated with tailored primary prophylaxis in Canada. *J Thromb Haemosts*. 2012;10(12):2494-2502.
13. Zwagemaker AF, Kloosterman FR, Hemke R, et al. Joint status of patients with nonsevere hemophilia A. *J Thromb Haemost*. 2022;20(5):1126-1137.
14. van Leeuwen FHP, van Bergen EDP, Timmer MA, et al. Magnetic resonance imaging evidence for subclinical joint bleeding in a Dutch population of people with severe hemophilia on prophylaxis. *J Thromb Haemost*. 2023;21(5):1156-1163.
15. Foppen W, van der Schaaf IC, Beek FJA, Mali WPTM, Fischer K. MRI predicts 5-year joint bleeding and development of arthropathy on radiographs in hemophilia. *Blood Adv*. 2020;4(1):113-121.
16. Stimec J, Dover S, Pullenayegum E, et al. Magnetic resonance imaging in boys with severe hemophilia A: serial and end-of-study findings from the Canadian Hemophilia Primary Prophylaxis Study. *Res Pract Thromb Haemost*. 2021;5(7):e12565.
17. Foppen W, van der Schaaf ICC, Witkamp TDD, Fischer K. Is joint effusion on MRI specific for haemophilia? *Haemophilia*. 2014;20(4):582-586.
18. Nguyen S, Lu X, Ma Y, Du J, Chang EY, von Drygalski A. Musculoskeletal ultrasound for intra-articular bleed detection: a highly sensitive imaging modality compared to conventional magnetic resonance imaging. *J Thromb Haemost*. 2018;16(14):490-499.
19. Regi SS, Livingstone RS, Kandagaddala M, et al. Ultrasound and magnetic resonance imaging for the detection of blood: an ex-vivo study. *Haemophilia*. 2021;27(3):488-493.
20. van Leeuwen FHP, Lena B, Zwanenburg JJM, et al. Detecting low blood concentrations in joints using T1 and T2 mapping at 1.5, 3, and 7 T: an in vitro study. *Eur Radiol Exp*. 2021;5(1):51.
21. van Leeuwen FHP, Lena B, van Bergen EDP, et al. Quantitative MRI assessment of joint effusion using T2-relaxometry at 3 Tesla: a feasibility and reproducibility study. *Skeletal Radiol*. 2024. doi:10.1007/s00256-024-04652-0
22. Culvenor AG, Øiestad BE, Hart HF, Stefanik JJ, Guermazi A, Crossley KM. Prevalence of knee osteoarthritis features on magnetic resonance imaging in asymptomatic uninjured adults: a systematic review and meta-analysis. *Br J Sports Med*. 2019;53(20):1268-1278.
23. Fischer K, de Kleijn P, Negrier C, et al. The association of haemophilic arthropathy with Health-Related Quality of Life: a post hoc analysis. *Haemophilia*. 2016;22(6):833-840.

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