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ORIGINAL ARTICLE

Magnetic resonance imaging evidence for subclinical joint bleeding in a Dutch population of people with severe hemophilia on prophylaxis

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Abstract

Background: Previous studies suggest that subclinical bleeding occurs in persons with hemophilia.

Objectives: The aim of this study was to investigate whether patients with lifelong access to prophylaxis showed signs of previous subclinical bleeding on magnetic resonance imaging (MRI) in joints without a history of joint bleeding.

Methods: This single-center cross-sectional study included persons with severe hemophilia A on prophylaxis, aged 16 to 33 years, with lifetime bleeding records available. Per participant, 1 index joint without a history of joint bleeding was evaluated with 3-Tesla MRI, including hemosiderin sensitive sequences. MRI scans were reviewed according to the International Prophylaxis Study Group (IPSG) additive MRI scale (range, 0-17/joint). Hemosiderin deposits with/without synovial hypertrophy were considered signs of previous subclinical bleeding. Additionally, physical examination was performed, followed by ultrasound examination according to the Hemophilia Early Arthropathy Detection with Ultrasound protocol.

Results: In 43 patients with a median age of 23.5 years, 43 joints (16 elbows, 13 knees, 14 ankles) without reported bleeds were evaluated with MRI. The median IPSG MRI score was 1 (range, 0-9). Signs of previous subclinical bleeding were observed in 7 of 43 joints (16%; 95% CI, 7-30): 7 of 7 joints showed hemosiderin deposits, with concomitant synovial hypertrophy in 2 of 7 joints. MRI changes were accompanied by swelling and ultrasound-detected synovial hypertrophy in 1 ankle only. None of the other joints showed abnormalities at physical examination and ultrasound.

Conclusion: In this study, 16% of the joints without reported bleeds showed signs of previous subclinical bleeding, providing evidence for subclinical bleeding in people with severe hemophilia with lifelong access to prophylaxis.

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Flora H. P. van Leeuwen and Eline D. P. van Bergen contributed equally to this study.

KEYWORDS
hemarthrosis, hemophilia, hemosiderin, magnetic resonance imaging, physical examination, ultrasound

1 | INTRODUCTION

Hemophilia is a rare X-linked genetic disorder, caused by a (functional) deficiency of coagulation factor VIII in hemophilia A and coagulation factor IX in hemophilia B. This deficiency results in an increased bleeding tendency. The hallmark, especially in severe hemophilia, is spontaneous or traumatic bleeding into the large synovial joints (mainly ankles, knees, and elbows). These recurrent provoked and spontaneous joint bleeds lead to joint damage, so-called hemophilic arthropathy, and cause considerable disease burden [1].

Multifactorial mechanisms of blood-induced joint damage have been described. When blood enters the joint, the synovial lining cells clear it from the joint cavity. In case of recurrent or ongoing bleeding, the synovial capacity to remove blood is exceeded. Subsequently, erythrocyte-derived iron accumulates as synovial hemosiderin deposits. The hemosiderin deposits induce synovial inflammation and proliferation, which are known predictors of recurrent bleeding and subsequent hemophilic arthropathy development [2,3].

Hemophilia treatment aims at preventing (joint) bleeds. Factor (trough) levels and records of bleeds are used to monitor and tailor treatment. The joint status is traditionally assessed by clinical outcome measures such as patient-reported outcomes and physical examination [4]. Since the introduction of prophylactic clotting factor replacement therapy, the number of clinically overt joint bleeds has decreased. Nijdam et al. [5] compared patients that stopped and continued prophylaxis and observed long-term joint deterioration in patients that had stopped their prophylaxis, despite comparable low bleeding rates and patient-reported outcomes. We hypothesize that this joint damage progression is because of subclinical bleeding and/or inflammation and underreporting of bleeds by the patient. This subclinical bleeding and inflammation theory is based on the observation of (presumably blood-induced) joint changes in the absence of clinically evident joint bleeds in the past [6–8].

In addition to clinically overt bleeds, subclinical bleeding or ongoing inflammation after a bleed may negatively affect joint outcome. The current outcome measures are unable to detect subclinical joint damage and may give the false suggestion of the absence of early joint changes [9–12]. Magnetic resonance imaging (MRI) is the reference standard for imaging of the synovium and iron/hemosiderin deposits [4,9]. Especially gradient echo sequences are known to be sensitive for the detection of hemosiderin because of the susceptibility artefacts that the iron-containing heme creates on the MR images [13]. As such, MRI is useful to evaluate joint health in studies with new treatment modalities (eg, emicizumab and gene therapy), as more sensitive joint outcome measures are required with the low bleeding rates reported [14,15].

Essentials

- Subclinical joint bleeding in hemophilia is previously reported, yet systematic evaluation lacks.
- Magnetic resonance imaging was used to assess subclinical bleeding in people with severe hemophilia A on prophylaxis.
- Hemosiderin deposits were observed in 16% of 43 joints without a history of bleeding.
- These magnetic resonance imaging findings provide evidence for subclinical bleeding despite prophylaxis.

This study aimed to provide evidence for subclinical bleeding in people with severe hemophilia with lifelong access to prophylaxis. We investigated the occurrence of signs of previous subclinical bleeds on MRI in joints without a history of joint bleeding in Dutch adolescents and adults with severe hemophilia A on prophylaxis.

2 | METHODS

2.1 | Study design and population

The Detecting Subclinical Joint BlEedinG and INflammation in Hemophilia study (BEGIN study) is a cross-sectional study evaluating signs of subclinical bleeding and inflammation in people with severe hemophilia A of 16 years and older, born after 1969, without recent joint bleeds nor a (history of) factor FVIII inhibitors who attended the Van Creveldkliniek (UMC Utrecht) for a routine follow-up visit from December 2019 until March 2022. The BEGIN study was approved by the institutional medical ethical review board (19-273 – BEGIN). All study participants gave written informed consent. For the present study, a subset of patients was evaluated with lifelong data on bleeding and treatment available.

Patients of the BEGIN study were eligible for inclusion in the present substudy if they had severe hemophilia A, were 16 years or older, and born after January 1, 1988. Patients had to have lifelong access to prophylaxis and had to be on prophylaxis for at least 12 months before inclusion [16,17]. They were included if they had at least 1 elbow, knee, or ankle without a history of joint bleeding according to their lifetime bleeding records. Patients were excluded if they had a history of a FVIII inhibitor (≥5 Bethesda Units [BU] at any time or 1–5 BU for ≥1 year), or contraindications for MRI (eg, claustrophobia, metal, or electronic implants that were incompatible with MRI).

2.2 | Study procedures

Patients were assessed by MRI, and additionally by physical examination and ultrasound within 24 hours of the MRI scan. For all patients, lifetime bleeding records were retrospectively searched to identify 1 joint (elbow, knee, or ankle) without a history of joint bleeding to assess with MRI. In case a patient had multiple joints without a history of joint bleeding, assessing an ankle was preferred over assessing a knee, and assessing a knee was preferred over assessing an elbow, since ankles are the most affected joints, followed by knees and the elbows [18,19]. We used a 3-Tesla MRI scanner (Philips Achieva) with joint-specific coils to assess knees and ankles (Philips Achieva), and a small extremity coil (Philips Achieva) to assess elbows. The MRI examination was performed without gadolinium contrast administration and included gradient echo sequences for optimal hemosiderin detection. Total scanning time was ~30 minutes. Detailed MRI protocols are available in Supplementary Table S1. MRI scans were reviewed according to the International Prophylaxis Study Group (IPSG) additive MRI scale by a single musculoskeletal radiologist with 10 years of experience with imaging of hemophilic arthropathy (W.F.). The IPSG additive MRI scale consists of a soft tissue domain, scoring effusion, synovial hypertrophy, and hemosiderin on a scale from 0 to 3, and a osteochondral domain, scoring surface erosions (0-2), subchondral cysts (0-2), and cartilage degradation (0-4) [20]. Additional to the conventional IPSG scoring based on the assessment of the elbows, knees, and tibiotalar ankle joints, the subtalar ankle joints were assessed separately using the items of the IPSG. The radiologist was blinded for all clinical information and the outcomes of the other study procedures. Hemosiderin deposits with or without synovial hypertrophy were considered signs of previous subclinical bleeding.

Additional physical examination assessed joint swelling and warmth of elbows, knees, and ankles (index joints). Joint swelling was reported according to the Hemophilia Joint Health Score (HJHS) 2.1 [21]. Warmth of the joint was reported as present or absent compared to the contralateral side. Ultrasound assessment of the index joints was performed according to the Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US) protocol [22], with additional assessment of synovial hyperemia using power Doppler assessment that was reported according to the Joint tissue Activity and Damage Exam protocol [23]. Physical examination and ultrasound assessment were performed or supervised by a physiotherapist trained in the use of the HJHS and ultrasound assessments with 9 years of experience in hemophilia care (M.T.). Physical examination and ultrasound assessment were performed without knowledge of the MRI scan findings.

2.3 | Data collection

At inclusion, age, annualized joint bleeding rate over the 5 years before inclusion (AJBR), type of prophylaxis (clotting factor replacement therapy or emicizumab), and the last reported total HJHS were extracted from the electronic patient records. Adherence to prophylaxis was determined as actual clotting factor consumption compared to prescribed clotting factor consumption during 1 year before inclusion. Patients who used <75% of the prescribed dose were considered as nonadherent. The most recent X-rays of all 6 index joints in each of the 43 patients (median time window, 3 years; range, 0-7) were evaluated according to the Pettersson scores by 1 radiologist (W.F.) using a reference atlas for scoring [24,25]. For all joints that were assessed with MRI, patient records were checked for reports of peri-articular bleeds and joint complaints not defined as intra-articular bleeding.

2.4 | Analysis

Patient and joint characteristics were reported as medians with ranges for continuous variables and as frequencies with percentages for categorical or dichotomous variables. Signs of previous subclinical bleeding on MRI were dichotomized as present or absent for all MRI scans. The proportions of joints with signs of previous subclinical bleeding on MRI and joints with osteochondral abnormalities were calculated. Occurrence of abnormalities at physical examination and ultrasound were compared between groups with and without signs of previous subclinical bleeding on MRI. Patients on continuous prophylaxis 12 months before inclusion were compared with patients on intermittent prophylaxis 12 months before inclusion for signs of subclinical joint bleeding, IPSG MRI scores, and AJBRs. After obtaining informed consent and inclusion in the study, the patient's records could be thoroughly reviewed. This review identified 2 included patients who had a history of a transient high FVIII inhibitor that had been missed in screening for study eligibility. To evaluate the effect of 2 inadvertently included patients who turned out to have had transient high inhibitor titers (titer > 5BU), we compared the prevalence of signs of previous subclinical bleeding with and without these 2 patients. There is a possibility that minor bleeds were misclassified as peri-articular bleeds or nonjoint bleed-related complaints. Therefore, we compared the prevalence of signs of previous subclinical joint bleeding in all examined joints with the prevalence when leaving out any joints with reported peri-articular bleeds and/or complaints. The Exact method was used to calculate 95% CI of proportions. The Fisher's exact test or Man–Whitney *U* test was used to compare groups. All analyses were performed in RStudio (Version 1.3.1093).

3 | RESULTS

3.1 | Study population

Patients characteristics are available in Table 1. This study included 43 participants with severe hemophilia A. Data were complete except from X-rays of 2 elbows in 1 patient, in which an ankle was studied with MRI. Two patients with transient inhibitors were inadvertently included. The median age of the participants was 23.5 years (range, 16.5-33.2). The majority used prophylaxis with FVIII (n = 40, 93%), of

TABLE 1 Patient characteristics.

A) Patient characteristics (n = 43)	Median (range) or n (%)
Age (y)	23.5 (16.5-33.2)
AJBR	0.4 (0-6.8)
Prophylactic treatment	43 (100%)
FVIII	40 (93%)
Adherent to FVIII	32 (74%)
Nonadherent to FVIII (<75% of prophylaxis)	8 (19%)
Emicizumab	3 (7%)
B) Joint characteristics at patient level (sum of 6 index joints, n = 43)	
HJHS (range, 0-124)	0 (0-17)
HEAD-US score (ultrasound; range, 0-48)	1 (0-18)
Pettersson score (x ray; range, 0-78)	0 (0-19)

The percentage might not add up to 100% because of rounding; AJBR over a 5-year time period prior to inclusion; nonadherent: clotting factor consumption <75% of the prescribed dose.

AJBR, Annualized Joint Bleeding Rate; FVIII, factor VIII; HEAD-US, Hemophilia Early Arthropathy Detection with Ultrasound; HJHS, Hemophilia Joint Health Score.

which 32 were adherent and 8 were nonadherent to their prophylaxis. Three patients were on emicizumab prophylaxis; 1 patient was on emicizumab prophylaxis for 1 year and 2 patients switched from FVIII to emicizumab prophylaxis in the year before inclusion (4 and 6 months before inclusion). Joint bleeds were rare with an AJBR of 0.4. Joint status was good, with a median total HJHS score of 0, a median total HEAD-US score of 1, and a median total Pettersson score of 0. In these 43 patients, 16 elbows, 13 knees, and 14 ankles without a history of joint bleeding were selected and scanned. The joint characteristics of the joints that were evaluated with MRI are available in Table 2. The median IPSG MRI joint score of the 43 assessed joints was 1 (range, 0-9).

TABLE 2 Joint characteristics of joints without a history of bleeding that were evaluated with magnetic resonance imaging.

A) Joint characteristics (n = 43)	Median (range) or n (%)
Elbows	16 (37%)
Knees	13 (30%)
Ankles	14 (33%)
B) Joint status at joint level (n = 43)	
HJHS (range, 0-20)	0 (0-1)
HEAD-US score (ultrasound; range, 0-8)	0 (0-1)
Pettersson score (x ray; range, 0-13)	0 (0-0)
IPSG magnetic resonance imaging score (range, 0-17)	1 (0-9)

The percentage might not add up to 100% because of rounding; Annualized Joint Bleeding Rate over a 5-year time period prior to inclusion.

HEAD-US, Hemophilia Early Arthropathy Detection with Ultrasound; HJHS, Hemophilia Joint Health Score; IPSG, International Prophylaxis Study Group.

3.2 | MRI findings

The MRI findings are summarized in Figure 1 and Supplementary Table S2. Signs of previous subclinical bleeding on MRI were observed in 7 of 43 joints (16%; 95% CI, 7-30). Ankles were most often affected (43%; 95% CI, 18-72), followed by elbows (6%; 95% CI, 0-30). The examined knees in this study showed no signs of previous subclinical bleeding.

Details on the joints with signs of previous subclinical bleeding on MRI are summarized in Table 3 and Figure 2 shows examples of observed signs of previous subclinical on MRI (hemosiderin deposits and synovial hypertrophy). Four ankles and 1 elbow showed small hemosiderin deposits, 1 ankle showed moderate hemosiderin deposits, and 1 ankle showed large deposits. Concomitant synovial hypertrophy was observed in 2 ankles (2 of 7 joints). In 1 ankle with subtalar hemosiderin deposits (1 of 7 joints), osteochondral changes were observed at the middle talocalcaneal facet. These osteochondral changes corresponded with the location of the hemosiderin deposits in this ankle. The other joints with signs of previous subclinical bleeding showed no osteochondral changes.

The MRI findings in joints without signs of previous subclinical bleeding are also included in Figure 1. In 4 joints without signs of previous subclinical bleeding, osteochondral changes were observed (9%; 95% CI, 3-22). The osteochondral changes in these joints were retropatellar fissures without other abnormalities in 3 knees and subtalar cartilage loss grade 2 with surface erosion grade 1 in 1 ankle. Additionally, simple joint effusion, which is a known nonhemophilia-specific item of the IPSG MRI scale [26], was observed in 23 of 43 joints (54%; 95% CI, 38-69). The amount of effusion varied from small (15 of 23 joints), to moderate (7 of 23 joints) to large effusion (1 of 23 joints).

3.3 | Comparison of MRI with physical examination and ultrasound

Abnormalities at physical examination and ultrasound were similar between the groups with and without signs of previous subclinical bleeding on MRI (1/7 versus 0/36, $p = .16$). Of the 7 joints with signs of previous subclinical bleeding, the ankle with large synovial hypertrophy, large hemosiderin deposits, and large effusion on MRI showed minimal swelling at physical examination and minimal synovial hypertrophy without hyperemia on ultrasound. The other 6 joints with signs of previous subclinical bleeding showed no abnormalities at physical examination nor on ultrasound. The findings of physical examination and ultrasound in the joints with signs of previous subclinical bleeding are available in Table 3. Of the 36 joints without signs

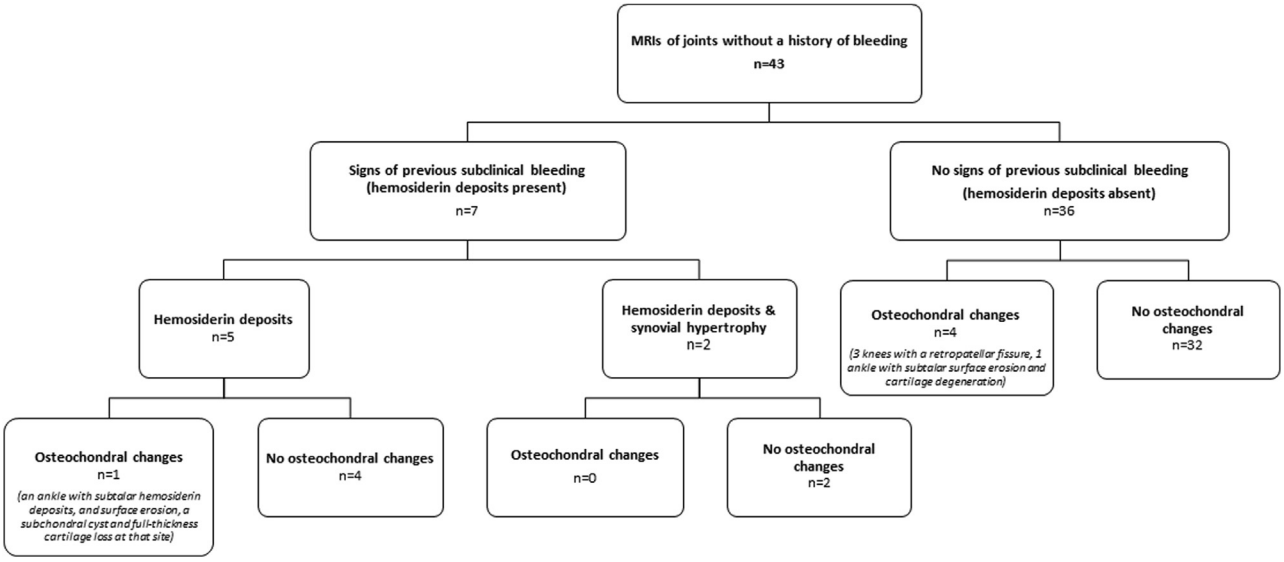

FIGURE 1 Flowchart summarizing magnetic resonance imaging findings in 43 joints without a history of joint bleeding.

of previous subclinical bleeding on MRI, none showed abnormalities at physical examination nor on ultrasound.

3.4 | Sensitivity analysis according to patient characteristics

Although all scanned joints were without intra-articular bleeds according to the lifetime bleed records, there is a possibility that minor bleeds were misclassified as peri-articular bleed or nonjoint bleed-related complaints. Therefore, we investigated whether hemosiderin deposits were present in joints with previous peri-articular complaints. We found previous peri-articular complaints in 5 of 43 joints (3 subcutaneous bleeds, 1 contusion, 1 tendinopathy). Hemosiderin was present in only 1 of 5 joints; an ankle with a registered subcutaneous bleed. The sensitivity analysis, leaving out the 5 joints with reported peri-articular complaints, resulted in a prevalence of signs of previous subclinical bleeding in 18% (95% CI, 7-36) of the joints. This was similar to the prevalence in all joints (16%; 95% CI, 7-30). Furthermore, the sensitivity analysis leaving out the 2 patients with a history of inhibitors resulted in a prevalence of previous subclinical bleeding (6 of 41 joints; 15%; 95% CI, 6-29) that did not significantly differ from the prevalence in all patients. Lastly, the sensitivity analyses on adherence, comparing patients who were adherent and nonadherent to FVIII prophylaxis during the last 12 months, showed that the prevalence of signs of previous subclinical bleeding (5/32 versus 2/8, p = .611), IPSG MRI scores (median 1 versus 1.5, p = .556) and AJBR (median 0.4 versus 0.4, p = .986) were similar.

TABLE 3 Details of joints with signs of previous subclinical bleeding on magnetic resonance imaging.

		MRI findings						
Age (y)	Joint	Hemosiderin deposits	Synovial hypertrophy	Effusion	Osteochondral changes	IPSG MRI score[b]	Physical examination	Ultrasound examination
25	Left elbow	Small	Absent	Small	Absent	2	Normal	Normal
18	Right ankle	Moderate	Small	Absent	Absent	3	Normal	Normal
21	Left ankle	Large	Large	Large	Absent	9	Mild swelling	Mild synovial hypertrophy without hyperemia
24	Left ankle	Small	Absent	Small	Absent	2	Normal	Normal
25	Left ankle	Small	Absent	Small	Absent	2	Normal	Normal
26	Left ankle	Small	Absent	Small	Absent	2	Normal	Normal
28	Left ankle	Small[a]	Absent	Small	Surface erosion: grade 1[a] Subchondral cysts: grade 1[a] Cartilage degeneration: grade 3[a]	1	Normal	Normal

IPSG, International Prophylaxis Study Group; MRI, magnetic resonance imaging.

[a] Joint changes at the subtalar joint.

[b] The IPSG MRI score is based only on tibiotalar joint changes of the ankle.

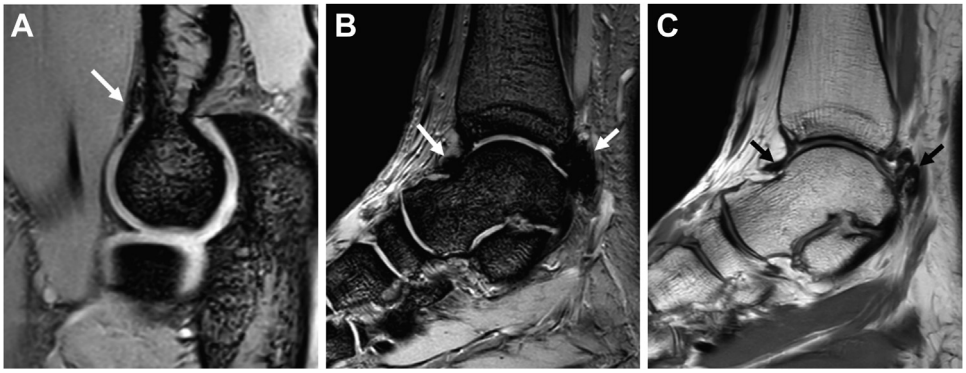

FIGURE 2 Examples of signs of previous subclinical bleeding on 3-Tesla magnetic resonance imaging scans of joints without a history of joint bleeding. (A) Sagittal T2 weighted (T2w) gradient echo (GE) image of an elbow showing subtle blooming artefacts because of hemosiderin deposits (white arrow). (B) Sagittal T2w GE image of an ankle with evident blooming artefacts because of larger hemosiderin deposits (white arrows). (C) Sagittal PD Dixon image of the same ankle showing that the hemosiderin deposits are located within a hypertrophied synovial membrane (black arrows) on the anterior and posterior side of the tibiotalar joint.

4 | DISCUSSION

In this cross-sectional study, we used MRI, ultrasound, and physical examination to investigate signs of previous subclinical bleeding in adolescents and adults with severe hemophilia A on prophylaxis. Signs of previous subclinical bleeding on MRI were observed in 16% (95% CI, 7-30) of the 43 examined joints without a history of joint bleeding. These MRI findings support the hypothesis that subclinical bleeding may occur despite prophylaxis. Noteworthy, abnormalities during physical examination and ultrasound were observed in only 1 joint (2%). This joint showed signs of previous subclinical bleeding on MRI.

4.1 | Strengths and limitations

Strengths of our study are parallel assessment of the joints with MRI, ultrasound, and physical examination, combined with 3-Tesla MRI scanning using protocols with gradient echo sequences. The relatively high field strength of the scanner combined with the properties of gradient echo sequences results in images that are highly sensitive for detecting small hemosiderin deposits [13]. Furthermore, all included patients had lifelong access to prophylaxis. Therefore, our study gives an indication of the occurrence of subclinical bleeding despite prophylactic treatment.

A limitation of our study is the retrospective review of patient records to determine which joint had no history of bleeding. Although lifetime bleed records were available, minor bleeds might have stayed unreported or might have been misclassified as nonjoint bleeding episode. However, missed bleeds can be considered subclinical bleeds by definition and therefore did not influence the evidence for subclinical joint bleeding in our study. Yet, misclassification of a joint bleed as peri-articular bleed or nonbleed related complaint might have led to overestimation of the prevalence of subclinical bleeding. However, a sensitivity analysis leaving out joints with any reported peri-articular complaints showed similar results. A second limitation is that lifetime adherence to prophylactic treatment cannot be verified. We determined adherence in the 12 months before inclusion to get an impression about the adherence in our population. The prevalence of subclinical joint bleeding was comparable in adherent and non-adherent patients. However, adherence to treatment remains a relevant point for future research and therapies.

Lastly, we evaluated only a single joint without a history of bleeding per patient and not every (subclinical) joint bleed may cause hemosiderin deposits or osteochondral changes. Therefore, the current study provides further evidence for the subclinical bleeding theory, without providing the prevalence of previous subclinical joint bleeding in all joints without a history of joint bleeding.

4.2 | Comparison with previous publications

Following the first description of MRI abnormalities in joints without reported bleeds by Manco-Johnson et al. [6], this phenomenon was reported in the Canadian CHPS study in children on tailored primary prophylaxis and a study in Dutch adults with nonsevere hemophilia [7,8,27]. The latter 2 studies reported the prevalence of hemosiderin deposits in joint without reported bleeds which allows comparison with our study. A MRI substudy of the CHPS study in 24 participants reported hemosiderin deposits in 17 of 65 joints without a history of joint bleeding (26%; 95% CI, 16-39) [7], which is comparable or slightly higher than the 16% (95% CI, 7-30) observed in 43 joints of 43 participants in the present study. This trend toward more joints with hemosiderin deposits may (partly) be explained by a higher risk of (subclinical) bleeding by the slower introduction of full prophylaxis in the CHPS study compared to the Dutch prophylaxis regimen [17]. Our findings were similar to those of the recent Dutch study in 51 adults with nonsevere (mild and moderate) hemophilia A that showed hemosiderin deposits in 21 of 149 joints without a history of joint bleeding (14%; 95% CI, 9%-21%) [8]. In this study, 88% of patients with soft tissue or osteochondral changes in joints without reported bleeds had mild hemophilia, but severity-specific data on hemosiderin deposits were not provided. Interestingly, only 19/80 joints (24%; 95%

CI, 15-36) with a history of bleeding in this study showed hemosiderin deposits, especially those with recent bleeding. This could be because of misclassification of bleeding or suggest total absorption of hemosiderin several years after joint bleeding.

In contrast to these 2 studies, the present study only scanned a single joint per patient, selecting the joint with the highest risk of subclinical bleeding. This may have led to an overestimation of the prevalence of hemosiderin in joints without reported bleeds in the present study. Besides, we cannot estimate the prevalence of subclinical bleeds that did not leave hemosiderin deposits in the joint, since such subclinical bleeds cannot (yet) be demonstrated. Furthermore, hemosiderin can also be observed in other diagnosis such as rheumatoid arthritis, ankylosing spondylitis, and Pigmented Villonodular Synovitis [28–30]. Although it is highly unlikely that this has influenced our results, since there was no evidence for these diagnoses in our patients.

The occurrence of osteochondral changes on MRI in patients without signs of previous subclinical bleeding in the current study is comparable to the occurrence of asymptomatic osteoarthritis in the general population. In our study, none of the 13 knees investigated showed signs of previous subclinical bleeding, whereas 3/13 knees showed cartilage defects (23%; 95% CI, 5-24). A meta-analysis of MRI features of osteoarthritis in asymptomatic uninjured knees of patients with a mean age <40 years reported a comparable prevalence estimate of cartilage defects in 11% of knees (95% CI, 6-17) [31]. This illustrates that cartilage abnormalities occur in the general population and therefore aging or common pathology should be considered when patient history, clinical presentation, or imaging findings do not match with blood-induced damage. The same applies to joint effusion on MRI, which is not hemophilia specific and also observed in healthy controls [26].

4.3 | Relevance for clinical practice and future research

This study identified that subclinical bleeding in patients on prophylaxis occurs and therefore supports the subclinical bleeding hypothesis. However, implementing MRI as a screening method in daily practice is difficult because of high costs, limited availability, time constraints, and the need for sedation in young children. Besides, signs of previous subclinical bleeding may not have direct clinical consequence. Nevertheless, detecting (previous) subclinical bleeding with MRI is important with the currently emerging novel therapies (emicizumab, gene therapy) and the clinically overt bleeds becoming increasingly rare [14,15]. Especially since physical examination and ultrasound were unable to detect signs of previous subclinical bleeding. Therefore, we would like to argue that comparing effectiveness of these new therapies based on outcome measures such as bleeding rates, factor levels, physical examination, and ultrasound is insufficient and that MRI-based outcomes should be considered to prove maximal joint protection in these trials.

5 | CONCLUSION

This study provides evidence for subclinical bleeding in adolescents and adults (age range, 16.5-33.2 years) with severe hemophilia A on prophylaxis. We observed signs of previous subclinical bleeding in 16% of the examined joints without a history of bleeding. Signs of previous subclinical bleeding were not associated with abnormalities at physical examination or ultrasound. MRI-based outcome measures should therefore be considered in the outcome assessment of novel nonfactor replacement therapies.

AUTHOR CONTRIBUTIONS

F.H.P.v.L. conducted formal analysis, investigation, data curation, and visualization and wrote the original draft of the manuscript. E.D.P.v.B. conducted formal analysis, investigation, data curation, and visualization and reviewed and edited the manuscript. M.A.T. conceptualized the study, conducted investigation, reviewed and edited the manuscript, supervised the conduct of the study. L.F.D.v.V. conceptualized the study, contributed in resources, reviewed and edited the manuscript, and supervised the conduct of the study. R.E.G.S. contributed in resources and reviewed and edited the manuscript. P.A.d.J. contributed in resources and reviewed and edited the manuscript. K.F. conceptualized the study, contributed in resources, reviewed and edited the manuscript, and supervised the conduct of the study. W.F. conceptualized the study, conducted investigation, reviewed and edited the manuscript, supervised the conduct of the study, and acquired funding for the study. The manuscript has been read and approved for submission to *JTHA* by all authors.

DECLARATION OF COMPETING INTERESTS

W.F. received research grants from Novo Nordisk and Pfizer, which were paid to the institution. M.A.T. received research grants from Novo Nordisk and SOBI and performed consultancy activities for SOBI, all paid to the institution. L.F.D.v.V. received research grants from CSL Behring and Grifols, and has performed consultancy for SOBI, CSL Behring, and Tremeau; all fees were 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. P.A.d.J. declares a research collaboration with Vifor Pharma and Philips Healthcare. E.D.P.v.B., F.H.P.v.L., and R.E.G.S. declare no conflicts of interest.

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SUPPLEMENTARY MATERIAL

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