REVIEW

Asymptomatic Joint Bleeding and Joint Health in Hemophilia: A Review of Variables, Methods, and Biomarkers

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Abstract: Joint health is a key contributor to quality of life in patients with hemophilia. However, variables that impact long-term joint outcomes have not been comprehensively defined. A systematic literature search identified publications relating to joint health in patients with hemophilia. Studies clearly show that early, sustained prophylaxis with factor replacements improves long-term joint outcomes. However, a subset of patients appear to develop arthropathy despite maintaining excellent bleeding outcomes, which suggests possible recurrent asymptomatic bleeding into the joints in these patients. Furthermore, limited data are available on how long-acting factor VIII and factor IX replacement therapies could impact long-term joint outcomes. Many variables were identified as potential indicators that a patient may develop hemophilic arthropathy, including genetic mutations, endogenous factor VIII and IX levels, bone health, and physical activity levels. Tools for the diagnosis and monitoring of hemophilic arthropathy are critical to detect early joint damage, so that management can be adjusted accordingly. Imaging techniques, particularly magnetic resonance imaging, can detect synovial changes, a strong predictor for the future development of hemophilic arthropathy. In addition, several biomarkers associated with cartilage and bone formation, vascularization, and angiogenesis could potentially identify the onset and progression of early joint damage. Since the development of hemophilic arthropathy is complex, a comprehensive therapeutic approach is necessary for the effective prevention of arthropathy in patients with hemophilia.

Keywords: hemophilia, asymptomatic bleeding, joint disease, hemarthrosis, hemophilic arthropathy, hemarthropathy

Introduction

Joint bleeds can lead to inflammation and destruction of the joint, which ultimately results in arthropathy, a significant morbidity in patients with hemophilia. Recurrent hemarthrosis results in the accumulation of hemosiderin, synovial inflammatory changes, cartilage degradation and, in late stages, joint destruction.[1,2] Hemophilic arthropathy is associated with increased pain, loss of employment, school absenteeism, and a reduction in physical wellbeing and quality of life.[3–7]

Effective prevention of joint deterioration is limited by the relatively limited knowledge of the pathogenesis of hemophilic arthropathy.[1] In addition, although commonly associated with severe disease, it is not currently possible to accurately predict which patients will develop hemophilic arthropathy as patients may develop arthropathy with few or no joint bleeds.[8–12] In patients with established joint

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damage, joint deterioration often progresses even if few or no further joint bleeds occur.[13] These observations suggest the occurrence of bleeding that is not detected by the patients, and this recurrent asymptomatic joint bleeding might contribute to the development of hemophilic arthropathy.[9,11,13]

Early prophylaxis with factor replacement concentrates can prevent joint bleeding, and thus the development of arthropathy.[12,14] Furthermore, identifying the variables that influence the progression of hemophilic arthropathy, including asymptomatic joint bleeding, may highlight modifiable aspects that could aid patients, or help to identify patients who may benefit from more intensive therapy in the future. Here, we firstly present the findings from a systematic literature review to identify variables that influence joint deterioration in patients with hemophilia. Secondly, we discuss methods to help identify patients with hemophilia who are at risk of joint deterioration and we consider the impact of long-acting factor replacement therapies on joint outcomes. We also consider which biomarkers may be associated with bone health in these patients. Lastly, we consider future research and practice directions for the prevention of arthropathy in patients with hemophilia.

Joint Outcomes in Hemophilia: A Systematic Literature Review
Methods
A systematic literature search was conducted in both EMBASE and PubMed, according to PRISMA guidelines,[15] on November 2018 and updated in July 2020 to identify variables that could influence the development of arthropathy, as assessed by joint scores, in patients with hemophilia. Search terms were designed to select publications according to the patient population, treatment administered, and outcomes reported. The search was limited to articles published in English, with no specified date range for PubMed and 1947 to present for EMBASE.

The following search term was used: Hemophilia AND (Magnetic Resonance Imaging OR Diagnostic imaging OR Ultrasonography OR Radiography OR Arthroscopy OR Synovectomy OR Arthralgia OR Hemarthrosis OR synovitis OR Synovial Fluid OR Synovial Membrane OR Hyperalgesia OR Brain Infarction OR Cerebral Hemorrhage OR Subclinical OR Silent OR Cartilage OR Hemochromatosis OR Iron OR Joint OR Articular OR

Table I Systematic Literature Review Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Original article	Review article or case study
Congenital hemophilia	Duplicate results
Included quantifiable	
information on joint health	Not in English
MRI scoring	Included joint interventions – such as
HEAD US scoring	physiotherapy, surgery or
Gilbert	radiosynovitis
Pettersson	Non-relevant disease model
ROM	Absence of hemophilia patients
HJHS/HJHS 2.1	
Arthropathy diagnosis code	
Orthopedic score (WFH)	
Petrini score	

Abbreviations: HEAD US, Hemophilia Early Arthropathy Detection with Ultrasound; HJHS, Hemophilia Joint Health Score; MRI, magnetic resonance imaging; ROM, range of motion; WFH, World Federation of Hemophilia.

Hemosiderin). The search terms were derived from an exploded MeSH term analysis that identified related terms.

All publications retrieved by this search strategy were individually assessed against pre-defined inclusion and exclusion criteria (Table 1). The aim was to identify original articles that looked at joint health outcomes assessed by joint scores. Publications underwent an initial screen based on the title and abstract using these inclusion and exclusion criteria. Potentially relevant publications then underwent a second screen based on the full text of the article. The relevant data from all eligible publications were collected and aggregated to allow further analysis.

Results
The initial search identified 5,380 results. Following the initial abstract and title screen, 861 articles were identified that met the initial screening criteria. The full-text screen identified 256 publications that measured arthropathy and recorded additional data on patients (Figure 1). Due to the wide variability in the outcomes considered, formal study quality assessment and meta-analytic evaluation were not performed.

Variables Influencing Joint Outcomes
The key variables that may influence joint outcomes highlighted by the literature search results were disease severity, gene mutations, bone mineral density (BMD), physical activity, and prophylaxis with factor replacement concentrates.
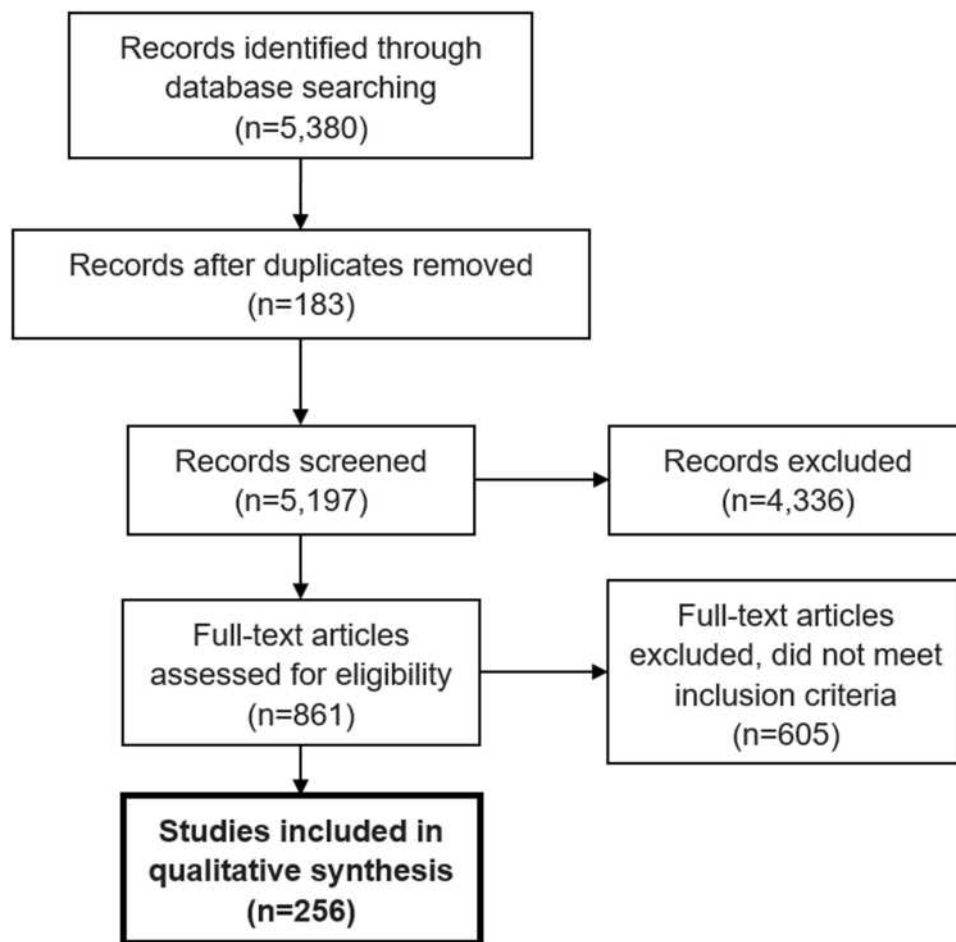
210

Journal of Blood Medicine 2021:12

Figure 1 PRISMA systematic literature review flow chart.

Disease Severity

Low endogenous FVIII/FIX activity levels (~1 IU/dl, 1% of normal) are known to be associated with higher rates of arthropathy due to the increased susceptibility to bleeding.[16–21] Patients with severe hemophilia (<1 IU/dl, <1% of normal) are more prone to joint damage than patients with mild or moderate hemophilia.[17] However, patients with moderate (1–5 IU/dl, 1–5% of normal) and mild (5–40 IU/dl, 5–40% of normal) hemophilia are still susceptible to developing arthropathy.[16,20,22,23] Factor levels of 1–3 IU/dl are now considered insufficient to fully prevent bleeding in all patients with hemophilia.[12] Even though the majority of patients with moderate hemophilia have fewer joint bleeds than patients with severe hemophilia, a subset of these patients (~30% of patients) experience bleeding and long-term joint damage.[16,22] Patients with mild hemophilia have a higher likelihood of developing chronic arthropathy than the general population and asymptomatic bleeding has been suggested as

its potential cause.[23] It is also notable that hemophilia carriers with factor activity levels >40 IU/dl (40% of normal) can experience decreases in joint range of motion (ROM) and structural joint changes.[18,19,21]

Gene Mutations

Several studies have correlated gene mutations with joint outcomes in patients with hemophilia (Table 2).[24–30] An investigation conducted in 14 hemophilia treatment centers in the United States found that a total of 613 single nucleotide polymorphism (SNP) markers were significantly correlated with ROM scores on at least two joint pairs.[24] This study also identified multiple inflammatory- or immune-related genes that were associated with arthropathy; SNPs in the NOD2 (associated with musculoskeletal manifestations in inflammatory bowel disease) and TLR10 (role in pathogen recognition and activation of innate immunity) genes were potentially strongly associated with arthropathy, but only a small number of patients carried the variant

Table 2 Gene Mutations and Genotypes Associated with Joint Health in Patients with Hemophilia

Gene/ Genotype	Mutation Type	Joint Health
Inflammatory and immune genes		
NOD2	Nonsynonymous	Increased risk of ROM abnormalities[24]
TLR10	Missense	Increased risk of ROM abnormalities[24]
HLA B27		Greater risk of developing chronic synovitis[27,28]
MTHFR 677TT		Higher number of affected joints[30]
MTHFR 1298AC		Higher degree of effusion[30]
TNFα-308GA		Increased number of subchondral cysts[30]
Genes encoding coagulation factors		
FVIII	Missense, nonsense, frameshift, intron 22 inversion	No association with HJHS or Gilbert score[25]
	Inversion, deletion, insertion, nonsense	Increased risk for a severe phenotype (>10 Pettersson score)[26]
FIX	Inversion, deletion, insertion, nonsense	Increased risk for a severe phenotype (>10 Pettersson score)[26]
Gene encoding homeostatic iron regulator protein		
HFE	C282Y, H63D	Increased number of hemarthrosis per year and number of affected joints[29]

Abbreviations: HJHS, Hemophilia Joint Health Score; ROM, range of motion.

alleles.[24] In another study, the underlying factor VIII (FVIII) mutation type (missense, nonsense, frameshift, intron 22 inversion) was not found to be significantly associated with joint deterioration in a cohort of hemophilia A patients with minimal access to hemostatic treatment.[25] In contrast, a study from India found that severe molecular defects of the FVIII or factor IX (FIX) gene were associated with disease severity, including poor joint outcomes, as patients with inversions, deletions, insertions and nonsense mutations had an approximate four-fold increased risk of having a severe disease phenotype.[26] Additionally, functional polymorphisms in the FVIII gene also affect the

phenotype; for example, patients with an FVII353Q allele had an increased risk of a severe phenotype.[26] However, this study did not identify any significant association with inflammatory or immunoregulatory cytokines. Two publications noted that HLA B27 mutations (associated with seronegative spondyloarthritis) were correlated with synovitis and arthropathy[27,28] and another reported that HFE mutations (associated with hemochromatosis), resulting in reduced iron absorption, contributed to the development of arthropathy.[29] A small study reported that patients with the MTHFR variants MTHFR 677TT or MTHFR 1298AC had a higher number of affected joints or a higher degree of effusion, respectively, compared to patients with other genotypes.[30] Furthermore, this study also found a positive association between genetic biomarkers related to inflammation and number of subchondral cysts.

Prophylaxis

Publications largely agreed that prophylaxis with factor replacement therapy reduces the rate of arthropathy development compared to episodic treatment.[8,14,31–38] Several publications showed that an early start to prophylaxis (before 2–3 years of age) reduces the risk of developing arthropathy.[33,35,36,39–42] However, it has been reported that early prophylaxis is not sufficient to completely prevent joint damage.[8–10,42] Prophylaxis initiated later in a patient's life has been shown to still provide benefits over episodic treatment with lower bleeding rates and improved joint health over time.[14,34,35] However, no reduction in structural arthropathy progression was observed, suggesting that pre-existing joint arthropathy may be irreversible,[14] further emphasizing the importance of primary prophylaxis. Continued prophylaxis also appears to be important; patients who stopped prophylaxis in adulthood showed similar bleeding rates to those on prophylaxis but had significantly higher rates of arthropathy over time.[43,44]

Bone Mineral Density and Physical Activity

Several studies found that low BMD correlated with arthropathy.[45–55] It has been suggested that the chronic pain associated with arthropathy leads to reduced mobility and an avoidance of weight-bearing activity, ultimately resulting in decreased BMD.[45–53] Overall, studies indicated that physical activity did not negatively affect joint health and may even improve joint health in patients with

hemophilia.[56–59] This may be due to improved muscle strength, balance and co-ordination seen in patients who maintain physical activity.

Identification of Patients with Hemophilia at Risk of Joint Deterioration
Imaging

Magnetic resonance imaging (MRI) is considered the most sensitive measure for joint assessment.[13] MRI provides detailed joint images and can detect early damage (ie, synovial hypertrophy) and soft tissue changes in joints as well as bleeds (Table 3).[13,60–62] MRI can also identify whether bleeds have occurred in a joint by detecting hemosiderin in the joint.[13,60,63,64] However, MRI can be expensive, time-consuming and difficult to access, and often requires sedation in children.[13,60] Ultrasound is less sensitive to early joint changes than MRI and is not able to discriminate between soft tissue types,[60,64] but is a cheaper imaging modality, more widely available, and easy to access.[13,64] Ultrasound can be used to detect synovial hypertrophy, and cartilage and bone surface abnormalities (Table 3).[13,60,61,63,65] In addition, it can also be used to rapidly assess multiple joints at once.[61] Patients only need to remain still for a short timeframe, which can be valuable when studying children's joints, and ultrasound can be incorporated into routine check-ups.[60,61,63,64] X-rays can also be used to assess joint deterioration and have demonstrated a good correlation with ultrasound and physical assessments, but low correlation with MRI findings.[66–68] X-rays show only late (ie, osteochondral) joint changes,[13] and when radiographic changes are detected, arthropathy is frequently already advanced.[13,62,65]

Clinical Joint Scores

Physical examination scales such as the Hemophilia Joint Health Score (HJHS) have been successfully used to assess joint outcomes, without requiring imaging techniques.[69–72] However, studies have found that the HJHS is not as sensitive as MRI or ultrasound, and thus assessment methods should be combined to generate a more detailed analysis of joints, until more accurate methods of assessment and scoring are available.[65,67] Smaller studies have also looked at using thermal imaging for inflammation, surface electromyography for muscle function and balance analysis for the lower limbs to detect early signs of joint deterioration.[73–75] These methods are not well characterized and are not routinely used for assessing joint outcomes.

Importantly, several studies have reported that bleeding rates do not or only weakly correlate with other outcomes such as MRI or HJHS,[8,67,71,76,77] and that joints deemed as "normal" according to physical examination or x-ray show abnormalities on MRI.[65,68,71] Therefore, joints that appear normal may be affected by asymptomatic bleeding. MRI is highly sensitive and can detect early joint damage, even before clinical symptoms manifest, and these MRI changes have been shown to strongly predict future development of arthropathy.[62] However, because MRI is not easily accessible, ultrasound may be a good affordable alternative.[13] Imaging techniques used in combination with thorough physical examination could provide accurate joint outcomes assessment tools for early diagnosis and subsequent monitoring of joint damage. For instance, MRI can be used to monitor normal joints in patients with hemophilia, including patients with mild hemophilia, in order to detect

Table 3 Properties of Magnetic Resonance Imaging (MRI) and Ultrasound

Properties	MRI	Ultrasound
Physiology and anatomy		
Detection of hemosiderin deposition	✓	✗
Detection of synovial inflammation	✓	✓
Detection of synovial hypertrophy and hyperplasia	✓	✓
Detection of soft tissue changes	✓	✓
Detection of osteochondral changes	✓	✓
Detection of joint effusions/hemarthrosis	✓	✓
Detection of cartilage and bone surface abnormalities	✓	✓
Detection of osteopenia	✓	✓
Methodology		
Visualization of internal joint structure and soft tissue types	✓	✗
Detection of different signal intensities	✓	✗
High spatial resolution	✓	✗
Not operator-dependent	✓	✗
Possible to scan multiple joints at once	✗	✓
Patient perspective		
No need for sedation in children	✗	✓
Fast	✗	✓
Health care systems		
Economical	✗	✓
Routine use	✗	✓
Readily available	✗	✓

Abbreviation: MRI, magnetic resonance imaging.

early arthropathic changes, which could allow for treatment adjustment and potentially prevent further joint deterioration, irreversible functional impairment, and future need for orthopedic surgery. Similarly, patients with mild damage could be monitored by ultrasound and patients with established disease could be monitored by joint scores and targeted imaging.

Impact of Long-Acting Factor Replacement Therapy on Joint Outcomes

Prophylaxis with long-acting factor replacement therapies in both hemophilia A and B has been associated with a reduced number of joint bleeds and resolution of target joints during clinical trials.[78] Recently, Zanon et al studied whether adherence to prophylaxis impacted on joint outcomes (HJHS) and involvement in physical activity.[79] The study reported a decrease in HJHS and the number of total target joints and an increase in physical activity levels in patients who had high adherence to prophylaxis compared to patients with no or low adherence.[79] Since poor adherence to prophylaxis might result in worsened joint outcomes, the use of long-acting products may help to avoid the low trough levels of FVIII and FIX that put patients at higher risk of bleeds (and then lead to joint problems).

The majority of the studies discussed in the systematic literature review that specifically investigated joint health and prophylaxis used standard-acting products. Recently, Malec et al compared joint health (HJHS) in patients with severe hemophilia A and B receiving standard-acting and long-acting products.[80] The study reported no differences in mean HJHS for either group of patients receiving standard-acting compared to those receiving long-acting products. However, joint health data were collected at a single time point, and thus the study did not assess the time of switch to long-acting products nor the status of joints over time after switching to long-acting products. Further data on arthropathy development in patients on long-acting products, as well as on patients switching from standard-acting to long-acting products, are needed.

Biomarkers and Bone Health in Patients with Hemophilia

Recurrent bleeding into the joints causes the synovium to hypertrophy in order to clear blood from the joint space, the synovium is overwhelmed and iron (hemosiderin) accumulates leading to synovial angiogenesis and inflammation.[1] The synovium produces pro-inflammatory cytokines and proteases, and this chronic proliferation of inflammatory cells causes the cartilage to breakdown. Furthermore, the constant presence of blood in the joint leads to bone changes, bone remodeling, loss of BMD and osteoporosis.[1] Consequently, biomarkers of inflammation, and cartilage, bone and synovium changes could provide a prospective method to detect and monitor asymptomatic joint bleeding as well as early joint damage.

Several studies have identified biomarkers in the blood or urine that could be indicative of joint deterioration. Table 4 provides an overview of these potential biomarkers of bone health. Proteins associated with inflammation (CRPM, hsCRP), cartilage destruction (C2M, CTX-II, COMP, ADAMTS5) and bone turnover (PINP, CTX-I) have been detected in hemophilia patients with joint disease.[81] Even though not all these biomarkers were correlated with radiological or physical joint assessments, the combination of C2M, CRPM and ADAMTS5 was able to distinguish hemophilia patients with joint disease from healthy controls with high accuracy.[81] Another study reported that several biomarkers of cartilage deterioration (CTX-II, C1,2C, CS-846 and COMP) correlated with radiographic joint damage in patients with hemophilic arthropathy, but bone biomarkers (CTX-I, C1,2C) did not.[82] One study found that serum levels of the key bone turnover markers sRANKL and OPG were significantly lower in patients with hemophilia than in healthy controls ($p<0.05$ and $p<0.001$, respectively), and these had an inverse correlation with joint outcomes (MRI and ultrasound).[83] The levels of serum sclerostin, another key regulator of bone formation, were significantly elevated in children with hemophilia versus healthy controls ($p=0.028$) and had a positive correlation with joint damage (HJHS); elevated levels of serum sclerostin in patients with hemophilia might be indicative of a high risk for developing osteoporosis.[52]

In another study, serum levels of the proinflammatory cytokine TNF-α were significantly elevated in patients with hemophilic arthropathy compared to healthy controls ($p<0.0001$).[84] Moreover, TNF-α levels were positively correlated with the number of joint bleeds, degree of synovial hypertrophy, and clinical and ultrasound joint outcomes. The authors suggest that TNF-α is involved in the progression of hemophilic arthropathy and could be a suitable biomarker to detect joint deterioration in patients with hemophilia.[84] However, TNF-α is an acute phase inflammatory marker that is elevated in a range of conditions, including rheumatoid arthritis, and as such is not specific to hemophilic

Table 4 Potential Biomarkers of Bone Health

Biomarkers	Decreased Levels in Patients with Hemophilia vs Healthy Controls	Increased Levels in Patients with Hemophilia vs Healthy Controls	Significant Correlation with Joint Scores
Inflammation	CRPM[81]	hsCRP[81] TNF-α[84]	TNF-α[84]
Cartilage destruction	ADAMTS5[81]	C2M[81] CTX-II[81] COMP[81]	CTX-II[81,82] C1,2C[82] CS-846[82] COMP[82]
Bone turnover	PINP[81] sRANKL[83] OPG[83]	CTX-I[81] Sclerostin[52]	sRANKL[83] OPG[83] Sclerostin[52]
Vascularization and angiogenesis		Microvascular density[88] VEGF expression[87,88] VEGFA[87] SDF-1α[87] MMP-9[87] HIF-1α[87] VEGFR1/CD11b[87] CD34/VEGFR1[87] VEGF/CD68[87] VEGFR2/AC133[87]	
Others	VitaminD[90–92]		Iron accumulation in cartilage[86] VitaminD[90–92]

arthropathy.[85] Iron accumulation in cartilage is another biomarker that has been shown to correlate with joint damage and progression of hemophilic arthropathy, further it has the advantage of being easily detected with MRI T2* sequences.[86] The development and validation of iron quantification MRI methods could assist in detecting asymptomatic joint bleeding, and provide a tool to evaluate and adjust treatment in patients with hemophilia.[86]

Vascularization and angiogenesis have been found to be increased in patients with joint damage. One study found that proangiogenic factors and proangiogenic macrophage/monocyte cells were up-regulated in patients with joint disease and expression of VEGFR2/AC133 endothelial progenitor cells and CD34/VEGFR1 hematopoietic progenitor cells were increased.[87] Sera from patients with joint damage induced an angiogenic response in endothelial cells, while peripheral blood mononuclear cells from these subjects induced synovial cell proliferation.[87] In another study, microvascular density and VEGF expression were significantly increased (p<0.005 and p=0.02, respectively) in synovial tissue from patients with hemophilic arthropathy compared to healthy controls.[88]

As mentioned above, there is evidence of an association between hemophilic arthropathy and low BMD. Furthermore, it has been shown that FVIII or FIX deficiency results in reduced BMD, with a quarter of patients with hemophilia having osteoporosis.[89] Low vitamin D levels have also been associated with decreased BMD, physical activity, quality of life and poor joint health.[90–92] These studies suggest that routine assessment of serum levels of vitamin D could guide early diagnosis of joint damage and treatment in patients with hemophilia, particularly in children. In patients with hemophilia, prevention of poor bone health should include primary prophylaxis, a diet rich in calcium and vitamin D, physiotherapy, and weight-bearing physical activities.[52,89–91]

Prevention of Arthropathy in Patients with Hemophilia: Future Directions in Research and Practice

There is robust evidence that prophylaxis with factor replacement therapies reduces the number of joint bleeds

and rate of arthropathy development; however, the optimal trough level to protect patients from joint damage has not been determined yet. Furthermore, factor replacement alone may not be sufficient to prevent joint damage. A recent study by Zhou et al reported that joint bleeding events were not associated with time spent below certain clotting factor thresholds, and that vascularity changes also played a role in joint bleeding.[93] Currently, an ongoing clinical trial (NCT03358836) is studying whether a long-acting FIX product with an intended trough level of >10% could provide better joint protection in patients with severe hemophilia B than the standard trough of 1% FIX. This study will also evaluate the early diagnosis of joint damage using ultrasound. The results from this study will be important, particularly since recent World Federation of Hemophilia guidelines have deemed factor trough levels of 1–3% insufficient to fully prevent bleeding in all patients with hemophilia.[12] However, results are not expected until 2027.

As previously discussed, several studies have identified potential targets for the prevention and treatment of arthropathy in patients with hemophilia, including cartilage iron, inflammation, bone remodeling, cartilage regeneration and vascular remodeling. Accordingly, a pilot study of the safety and efficacy of local anti-VEGF therapy with intra-articular bevacizumab (Avastin®) for prevention of recurrent hemarthroses at target joints is currently ongoing in Taiwan in patients with chronic hemophilic synovitis and was due for completion in late 2020 (NCT02060305).

Furthermore, it is not yet known what level of joint protection emergent non-factor replacement therapies and gene therapy may provide. Some of these products are still in development and it will be some time until their effects on joint health, and prevention and treatment of hemophilic arthropathy can be analyzed.

Finally, physiotherapists play a valuable role in assessing patients' joint status and in aiding recovery of function after a joint bleed, but many centers lack a dedicated hemophilia physiotherapist. Dedicated hemophilia 'joint assessors' could play an important role in providing dedicated time for thorough physical examination and joint scores, and in monitoring the progress of joint deterioration. Currently, home-based physiotherapy programs are being evaluated in people with hemophilia as an inexpensive accessible intervention with the potential to improve joint health.[94,95] Individualized home-based exercise programs, with access to online/virtual tools and support from physiotherapists, have been positively received with encouraging results.[94–96] Future randomized controlled clinical trials will be able to provide evidence of the clinical efficacy of such programs.

Conclusions

Currently, the best treatment option for patients with hemophilia is prophylaxis, particularly in young patients for whom primary prophylaxis is vital for the prevention of bleeding and to promote healthy joints. However, maintaining factor levels over a certain threshold does not fully prevent joint bleeds. Joint abnormalities and reduction of ROM have been reported even in patients who started prophylaxis early, in patients with mild hemophilia and in hemophilia carriers. In these cases, the occurrence of asymptomatic joint bleeding might be undetected for a significant amount of time before it is identified, and intervention can be provided. Therefore, early detection of changes in "normal" joints becomes crucial. To this end, sensitive diagnostic methods such as MRI or ultrasound are critical for early diagnosis of joint damage, monitoring of deterioration and treatment guidance, particularly in patients with normal physical and x-ray assessments. Although specific biomarkers of joint damage are still lacking, a few candidates such as cartilage iron, and inflammatory, cartilage destruction and bone formation factors have the potential to become novel targets for early diagnosis, prevention and treatment of joint damage in patients with hemophilia. The future of treatment of patients with hemophilia may be a therapeutic approach consisting of primary prophylaxis with factor replacement, calcium and vitamin D supplementation, physiotherapy and weight-bearing exercise programs, together with routine monitoring of cartilage iron, vitamin D, and key inflammatory and bone formation biomarker levels, as well as joint status with sensitive imaging and physical assessment tools.

Abbreviations

BMD, bone mineral density; FVIII, factor VIII; FIX, factor IX; HJHS, Hemophilia Joint Health Score; MRI, magnetic resonance imaging; ROM, range of motion; SNP, single nucleotide polymorphism.

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