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Review

Unmet needs in hemophilic arthropathy

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ABSTRACT

Hemophilia A and B are rare X-linked bleeding disorders caused by coagulation factor deficiencies, leading to joint bleeding, synovial hypertrophy and chronic hemophilic arthropathy marked by progressive cartilage and bone damage. Musculoskeletal issues remain the primary source of morbidity in people with hemophilia (PwH). Despite significant advances in prophylactic therapies, joint pain, functional limitations, and deterioration persist. The long-term impact of novel treatments on joint health and physical activity levels remains incompletely understood. Early detection and prevention of damage is challenging, highlighting the need for highly sensitive diagnostic tools to identify subclinical changes before irreversible damage occurs. Pain management, currently adapted from other conditions, does not fully meet the unique needs of PwH. Research into targeted pain relief, synovial hypertrophy management, and cartilage regeneration is crucial. Addressing unmet needs in diagnosis, treatment, and management requires collaboration between clinical and research communities to improve care effectiveness and enhance the quality of life for PwH.

1. Introduction

Hemophilia A and B are rare X-linked bleeding disorders caused by deficient or absent clotting factors VIII and IX, respectively. These disorders are classified according to the residual level of circulating clotting factor activity: severe (<1 IU/dL), moderate (1–5 IU/dL), and mild (5–40 IU/dL). Spontaneous joint bleeding is a hallmark of severe hemophilia and leads to synovial hypertrophy, which if left unchecked, results in chronic and debilitating hemophilic arthropathy, a condition characterized by progressive cartilage and bone destruction. Musculoskeletal complications remain the leading cause of morbidity in people with hemophilia (PwH) [1]. While early initiation of regular factor replacement therapy as prophylaxis to prevent bleeding has significantly reduced joint bleeding rates and improved the quality of life of PwH, joint pain, functional limitations and progressive joint deterioration remain ongoing challenges. Even a single episode of hemarthrosis can have lasting effects on joint health, highlighting the need for further advances in care. Despite transformative advances in treatment, including prophylactic regimens, extended half-life factor concentrates and non-factor therapies, critical gaps remain [2].

The current goal of hemophilia care is to provide PwH with not only the most normal life possible, but also the least burden possible, with the ultimate goal of a "hemophilia-free mind" [3].To achieve this goal, we must address three key unmet needs: (1) better diagnosis and treatment of bleeding to prevent complications and improved monitoring of joint health and its progression, (2) improved management of synovitis, the only reversible stage of arthropathy, to slow disease progression, and (3) better support for patients with irreversible osteochondral lesions to enhance mobility, flexibility, and muscle strength while reducing chronic pain and improving quality of life. (Fig. 1).

This review aims to explore these unmet needs through a comprehensive analysis of the existing literature and provide insights to guide future advances in hemophilia care.

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2. Unmet needs in the diagnosis of joint bleeding, early arthropathy detection, monitoring of joint health and its progression

2.1. Pathophysiology of hemophilic arthropathy

A deeper understanding of the pathophysiology of hemophilic arthropathy is essential for the development of early diagnosis tools and targeted therapies for PwH. Repeated bleeding into the same joint triggers a cascade of pathological changes, ultimately leading to synovial hypertrophy, hemosiderin deposition, cartilage degradation, and alterations in the subchondral bone structure [4]. These processes contribute to the progressive joint damage seen in hemophilic arthropathy, beginning with reversible synovitis and progressing to irreversible osteochondral lesions. In vitro and in vivo studies, including animal models, have shed light on the direct effects of blood on the synovium and cartilage. The presence of both mononuclear cells and red blood cells in the joint space sets off a complex interplay of inflammatory and degenerative mechanisms (Fig. 2). The breakdown of red blood cells releases iron, which accumulates in the synovium and surrounding tissues, exacerbating the local inflammatory response [5]. Hypervascularization of the synovial tissue, a hallmark of hemophilic synovitis, increases the risk of recurrent bleeding events, further perpetuating the cycle of joint damage.

Inflammatory changes within the joint play a pivotal role in cartilage degradation. Activated synovial cells and infiltrating immune cells release pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and TNF-α, along with tissue-degrading enzymes like matrix metalloproteinases (MMPs) [6]. These molecules break down the extracellular matrix of cartilage, compromising its structural integrity and leading to progressive joint destruction [7]. Recent research on hemophilia has highlighted the specific role of iron in exacerbating cartilage injury. A study examining chondrocytes from PwH with hemarthrosis revealed that iron dysregulation directly affects cartilage health by modulating the expression of key regulatory factors, such as fibroblast growth factor 23 (FGF23) and SRY-box Transcription Factor 9 (SOX9) [8]. FGF23, involved in phosphate homeostasis and bone metabolism, and SOX9, a critical transcription factor for cartilage development and maintenance, are both disrupted in the presence of excess iron. This dysregulation accelerates chondrocyte dysfunction, further contributing to cartilage degradation.

These insights highlight the complex nature of hemophilic arthropathy, where mechanical damage, inflammation, and metabolic dysregulation converge to drive joint destruction.

2.1.1. Limitations of conventional indicators of joint bleeding

Prophylaxis is the standard of care in hemophilia treatment, aimed at preventing bleeding and protecting joint health by minimizing recurrent bleeding. The introduction of PK-guided prophylaxis has allowed personalized treatment regimens to optimize efficacy. More recently, extended and ultra-extended half-life factor products have improved bleeding protection by maintaining higher trough levels in both hemophilia A and B. In parallel, the emergence of subcutaneous non-factor therapies has significantly reduced disease burden while providing effective bleeding prevention, with most agents achieving an annual bleeding rate (ABR) close to zero. The efficacy of available drugs to prevent bleeding and in particular joint bleeding in PwH is without question however long-term data on the prevention of joint damage, possibly stemming from unrecognized, subclinical bleeding is yet to be demonstrated.

In most cases, annual joint bleeding rates (AJBR) are based on patient self-report, which is highly variable due to its subjective nature [9]. Unlike objective assessments using standardized, measurable criteria, self-reported data can be influenced by recall bias, variations in individual perception of bleeding events and pain, and differences in patient awareness of subclinical or minor bleeding. This variability highlights the need for more reliable and standardized methods to accurately assess joint bleeding rates and their impact on long-term joint health.

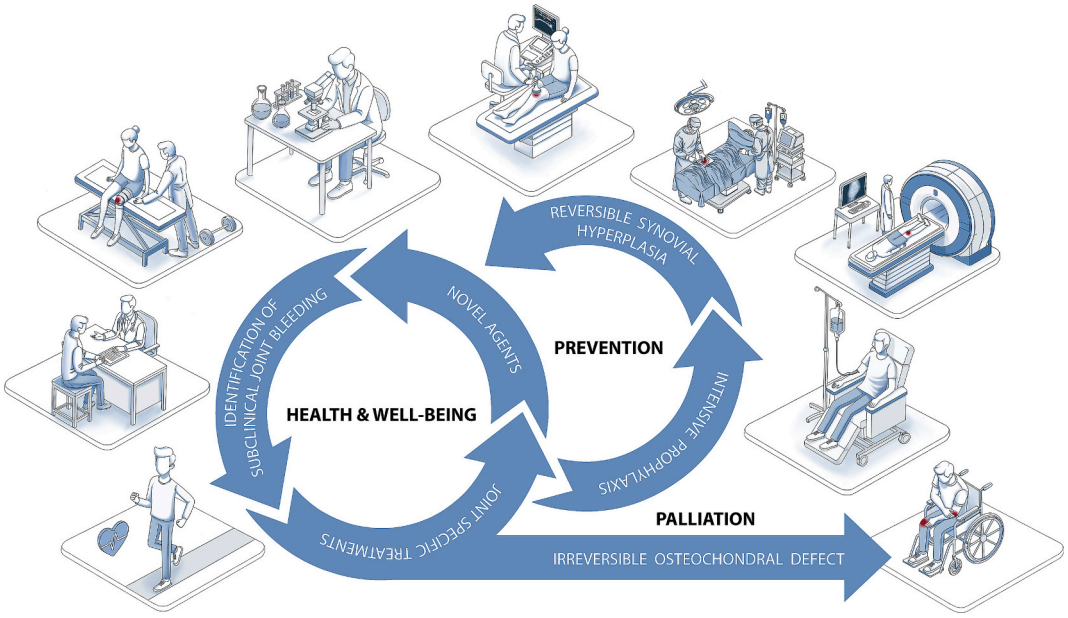

Fig. 1. Maintenance of healthy joints. The health and well-being of people living with hemophilia is determined in large part by maintaining healthy joints, free of bleeding and pain and allowing for normal motion and participation in activities. Identification of and adequate control of bleeding is a key to achieving this goal. The introduction of novel agents to prevent and treat bleeding has improved the outcomes but joint specific treatments remain a goal for the community. Use of ultrasonography at the point of care facilitates rapid identification of bleeding however implementation of biomarkers to identify subclinical bleeding would be a welcomed addition to the management of people with hemophilia. Once bleeding into the joint occurs, synovial hyperplasia ensues which can be reversed by intensive medical prophylaxis and physiotherapy. If not controlled, an irreversible chronic arthropathy develops characterized by chronic pain, limitations in range of motion, muscle loss, inability to participate and overall decrements in health-related quality of life. Osteochondral defects, the hallmark of irreversible joint damage, often require interventions to ablate the hyperactive synovium and/or replace the defective joint.

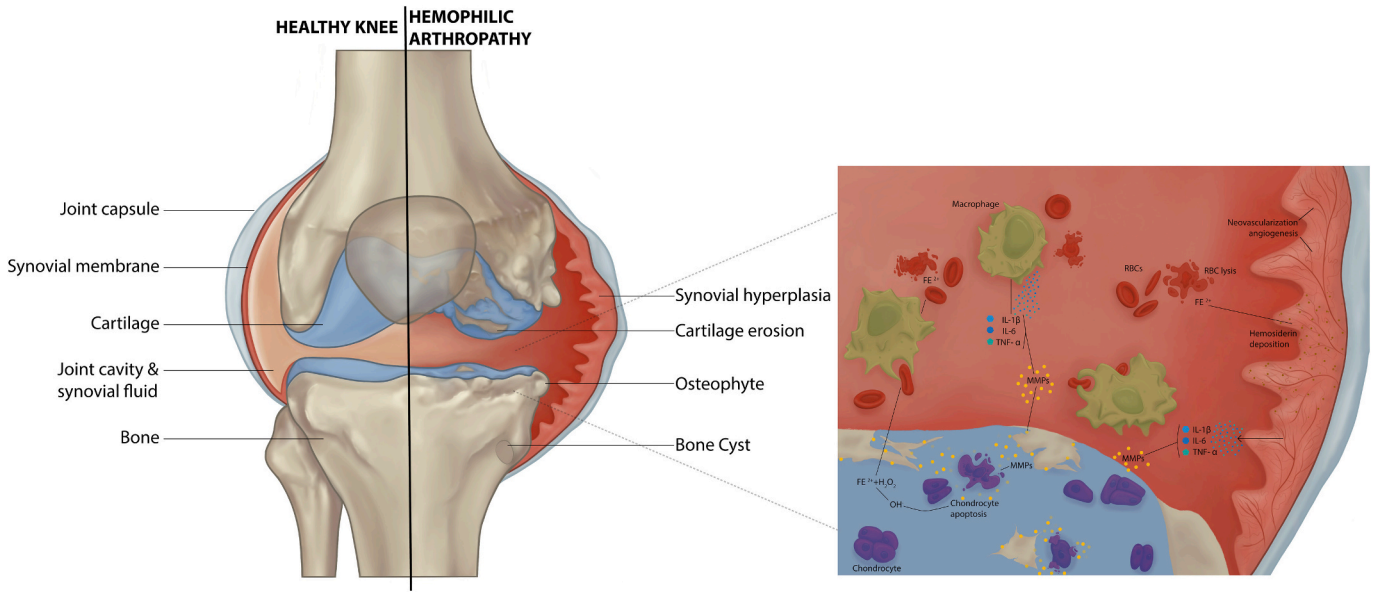

Fig. 2. The pathophysiology of joint damage in hemophilia. The panel on the left depicts a healthy knee joint while the right demonstrates the pathological changes that ensue following bleeding in the joint. Red blood cells release iron which stimulates synovial hyperplasia and is toxic to chondrocytes causing their apoptosis. Synovial hyperplasia is accompanied by increased vascularity of the synovium combined with a dense inflammatory infiltration with activated tissue macrophages leading to a local cytokine storm. Matrix metalloproteinases degrade the cartilage matrix causing structural insecurity. Cytokines, interleukins along with enzymes degrade cartilage and damage bone causing cyst and osteophyte formation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The progression of hemophilic arthropathy is strongly linked to the occurrence and frequency of joint bleeding. PwH treated for acute bleeding on-demand often experience 20 to 50 bleeding episodes per year [10], leading to early joint damage, while prophylaxis initiated at an early age can delay or even prevent joint disease in most cases [11]. However, the Joint Outcome Study showed that some children developed osteochondral damage despite no reported joint bleeding, while others with multiple bleeds showed no radiographic damage. Biological differences in the inflammatory milieu or angiogenic properties of individuals might underlie these phenotypic differences underscoring the imperative to prevent all episodes of bleeding [12,13].

2.2. Limitations of clinical tools for joint assessment

Joint assessment begins with a detailed history and clinical examination to identify the signs and symptoms of bleeding and joint damage. PwH typically recognize joint bleeding by the onset of acute pain, reduced range of motion, warmth, and swelling due to joint capsule distention and inflammation [14] however, pain perception varies [15] and bleeds may not always be confirmed by ultrasonography [16].

The Hemophilia Joint Health Score (HJHS) is widely used for joint assessment but has significant limitations. Its combination of structural (swelling, atrophy, crepitus) and functional (range of motion, pain, strength) measures complicate interpretation but also makes it a multidimensional tool. The HJHS lacks sensitivity to early changes like subclinical synovitis, detectable via ultrasound, with up to 40 % of PwH showing synovitis despite a zero-swelling score [9,17]. It also has a ceiling effect in advanced arthropathy, limiting its ability to track progression or treatment effects. Additionally, range of motion (ROM) assessments rely on normative tables that may miss subtle deviations in PwH, and inter-operator variability further affects consistency. Addressing these challenges requires standardized training, validation, and ongoing competency programs [18].

Recent advancements in assessing activity limitations in hemophilia have significantly improved measurement accuracy. While the Hemophilia Activities List (HAL) [19,20], a mainstay for two decades, has limitations in score interpretation, the newly developed ACTIVLIM-Hemo score [21], utilizing the Rasch model, offers a more precise and linear measure with superior psychometric properties. This advancement not only allows for objective comparisons across treatments but also facilitates comprehensive follow-up of PwH. However, for widespread adoption, broader validation is essential.

In addition to standardized scores, performance-based tests like the 6-min walk test and TUG test provide valuable insights, although they may not capture complex movements adequately [22]. Integrating these tests with imaging and clinical scoring could potentially enhance both diagnosis and treatment strategies, offering a more holistic approach to managing hemophilia-related activity limitations [23].

2.3. Limitations of imaging methods for joint assessment

The World Federation of Hemophilia (WFH) recommends a diagnostic approach for assessing joint pathology that combines clinical evaluation with imaging—ultrasound, radiography, and Magnetic Resonance Imaging (MRI)—to stage joint degeneration, assess severity, and monitor treatment response [24]. Despite its widespread use, conventional radiography has low sensitivity for early joint damage and soft tissue changes like synovitis, making it less effective for early diagnosis or short-term monitoring [25]. However, it remains valuable for assessing advanced joint pathology in adult PwH and is commonly used in preoperative and postoperative evaluations of joint replacement. The WFH endorses the Pettersson scoring system, which grades radiographic changes by severity [26]. Notably, radiography cannot detect the earliest stages of arthropathy.

MRI is the gold standard for joint evaluation, providing unmatched resolution of soft tissues, cartilage, synovium, and hemosiderin deposits [27]. The most widely used scoring methods are the Denver [28] and European [29,30] scales. MRI is particularly valuable for detecting early joint pathology and guiding clinical management. However, its use in practice remains inconsistent due to the lack of clear, evidence-based guidelines on indications, frequency, and optimal timing.

Limited accessibility, high costs, long scan times, and the need for sedation in children further restrict its routine use, reducing opportunities for early intervention and long-term monitoring [31].

Point-of-care ultrasound (POC-US) has become a key tool in evaluating the joints of PwH, offering accessibility, affordability, and the ability to detect early changes missed in clinical exams [32]. Its real-time imaging supports rapid decision-making, especially in resource-limited setting [33]. Several standardized scoring protocols, including Hemophilia Early Arthropathy Detection with Ultrasound (HEAD-US), Joint tissue Activity and Damage Exam (JADE), and POC Musculoskeletal Ultrasound (POC MSKUS), have been developed to enhance its clinical utility. HEAD-US detects early structural changes and provides a semi-quantitative score for tracking joint abnormalities over time [34,35]. JADE refines this approach, classifying joint damage stages from acute inflammation to chronic deformities, aiming for global standardization [36]. POC MSKUS integrates findings across multiple joints into a unified scoring system, making it valuable for longitudinal studies and personalized treatment [37]. Future advancements will likely focus on refining these protocols [38], incorporating AI-driven automated scoring, and expanding use in underserved areas to improve outcomes [39,40]. Despite its advantages, POC-US has limitations. Evaluating complex joints like the ankle remains challenging due to intricate anatomy, overlapping structures, and limited acoustic windows, increasing the risk of misdiagnosis. Pediatric assessments add further complexity, as rapid growth and anatomical variability require protocol adaptations and refined interpretation criteria. Addressing these challenges requires enhanced operator training, especially for pediatric assessments. Combining POC-US with MRI and clinical evaluations offers a more comprehensive view of joint health. Standardized protocols, improved guidelines, and AI-assisted interpretation could further reduce variability, maximizing POC-US's diagnostic value. POC-US is highly operator-dependent, underscoring the need for robust training programs. However, training remains scarce, often industry-sponsored, with few qualified trainers worldwide. Additionally, the lack of a validated reference atlas covering both normal and pathological ultrasound findings limits standardization and reproducibility. To bridge these gaps, healthcare systems must invest in structured education, ongoing competency programs, and accessible reference materials to ensure consistent and accurate joint assessments [41]. Nevertheless, compared to MRI, ultrasound is significantly more affordable in terms of both equipment acquisition and maintenance, making it particularly suitable for use in low- and middle-income countries. Support initiatives from organizations such as the World Federation of Hemophilia (WFH) can further facilitate the provision of equipment and the training of healthcare professionals in musculoskeletal ultrasound. With appropriate training and practice, ultrasound can enable serial monitoring of joint health, complement clinical outcome scores, and support early diagnosis and intervention—at a stage when joint damage may still be reversible. It also provides objective insights into the effectiveness of treatment regimens.

In clinical practice, X-ray remains useful for detecting bone fractures in cases of acute joint pain and for assessing advanced osteochondral changes, such as joint surface irregularities, bone cysts, erosions, and joint space narrowing, in particular, as part of the preparation for orthopedic surgery. Musculoskeletal ultrasound is particularly valuable for addressing targeted clinical questions, including the presence or absence of intra-articular bleeding, synovial hypertrophy, joint effusion, and osteochondral damage. MRI provides the most detailed and comprehensive evaluation of soft tissues and cartilage. However, as previously discussed, each imaging modality has inherent limitations, and none currently provides optimal sensitivity for the early detection of joint involvement in PwH.

Robust assessment tools are essential for precise diagnosis and monitoring. A comprehensive approach combining MRI and POC-US, guided by standardized protocols, improves early detection and long-term outcomes. The ICF model offers a holistic framework by integrating activity limitations, participation, and environmental factors beyond structural and functional assessments. To ensure a more transversal evaluation of PwH, this approach should be widely adopted using psychometrically superior tools, enhancing reliability and sensitivity. Incorporating this multidimensional perspective into clinical practice fosters a deeper understanding of patient well-being and enables more effective, personalized care.

2.4. *Emerging biomarkers in hemophilic arthropathy*

Given these challenges, there is an urgent need for more precise and objective biomarkers to complement advanced imaging methods in assessing joint health.

Blood and urine biomarkers, including C-Reactive Protein Matrix Metalloproteinase-degraded (CRPM), Type II Collagen Matrix Metalloproteinase-degraded (C2M), C-Terminal Telopeptide of Type II Collagen (CTX-II), Cartilage Oligomeric Matrix Protein (COMP), A Disintegrin and Metalloproteinase with Thrombospondin Motifs 5 (ADAMTS5), and Procollagen Type I N-Terminal Propeptide (PINP), have been linked to joint deterioration and bone health in hemophilia. While not all correlate with imaging, combinations like C2M, CRPM, and ADAMTS 5 effectively differentiate joint disease from healthy controls [42–44]. Markers such as CTX-II and COMP correlate with radiographic damage, while bone markers like CTX-I show weaker associations [42–46]. Low soluble Receptor Activator of Nuclear Factor Kappa-B Ligand (sRANKL), osteoprotegerin (OPG), and elevated sclerostin levels in PwH are associated with joint damage and osteoporosis risk [47]. Tumor Necrosis Factor alpha (TNF-α) levels correlate with disease severity but lack specificity [48]. None of these biomarkers has been validated for routine clinical use. However, a simple, robust and easily administered test - with sufficient sensitivity and specificity for hemophilic arthropathy - that can detect early osteochondral changes before they are visible on imaging, using only a blood sample during routine clinical visits, would be invaluable in both diagnosing and monitoring joint damage.

Recently, circulating microRNAs have emerged as promising biomarkers for hemophilic arthropathy [49]. Widely used as diagnostic tools in oncology, cardiology and various bone-related disorders, microRNAs are small non-coding RNAs that regulate gene expression. They offer several practical advantages: they can be readily analyzed using standard techniques available in most hospital laboratories, and they exhibit high stability in biological fluids such as blood due to their resistance to RNAases. A recent proof-of-concept study identified two specific microRNAs as potential signatures of hemophilic arthropathy in patients with advanced joint disease [49].

The identification of circulating microRNA as biomarkers of hemophilic arthropathy also has the potential for the treatment of arthropathy using anti-microRNA oligonucleotides that may neutralize key microRNAs involved in the pathophysiology of hemophilic arthropathy.

All of these biomarkers currently remain research tools; none have yet been validated for routine clinical use in the diagnosis and monitoring of hemophilic arthropathy. Nonetheless, they hold promise as potential tools for early diagnosis and monitoring, as they are easy to perform, repeatable over time, non-invasive, and less costly than imaging techniques.

3. Unmet needs in the management of hypertrophic synovitis

Prophylaxis significantly reduces joint bleeding events and promotes long-term joint health. To effectively prevent joint damage, prophylaxis should ideally be initiated before joint disease develops and, whenever possible, before the first joint bleed [50]. Early initiation of individualized prophylaxis, coupled with patient education, engagement, and adherence, is crucial to achieving these therapeutic goals. However, despite adherence to current prophylaxis guidelines, recent data suggest that PwH continue to experience joint bleeding and deterioration during long-term follow-up. In such cases, tailored treatment strategies—such as intensified factor prophylaxis—are recommended, especially in the presence of synovitis [19,51]. A recent randomized, open-label clinical

trial demonstrated that intensive prophylaxis aiming for trough levels of 8–12 % resulted in an approximately fourfold higher rate of hypertrophic synovium reduction or resolution (35.9 % vs. 8.4 %) compared to standard prophylaxis targeting trough levels of 3–5 %. [52]. Data on the impact of non-factor therapies on the reduction or resolution of hypertrophic synovium are not yet available, and further studies are needed to evaluate their potential disease-modifying effects.

Historically, personalized prophylaxis in hemophilia has focused on intensifying treatment regimens based on the frequency of joint bleeds. Over the past 15 years, pharmacokinetic (PK)-guided dosing has become the standard, enabling prophylaxis to be tailored to the individual needs of patients. Early adaptations involved increasing the frequency of injections or the dose of coagulation factors. With the introduction of extended half-life (EHL) factors, PwH and target joints transitioned from standard molecules to EHLs [53]. More recently, the focus has shifted from EHLs to non-factor therapies that maintain a stable hemostatic state [54]. There is now growing interest in transitioning PwH on EHL therapies to second-generation mimetics or ultra-extended FVIII formulations [55]. While advancements in treatment potency and efficacy continue, the primary focus for hematologists remains the prevention of bleeding events [56]. However, for PwH with established joint damage, current treatments primarily address bleeding and do not directly target underlying synovitis or cartilage degradation. Currently, there are no therapies specifically designed to target synovial inflammation and cartilage preservation in hemophilia. Bridging this gap presents a critical opportunity for further innovation in hemophilia care, with the potential to address the underlying mechanisms of joint damage and improve long-term outcomes for patients.

Complex mechanisms of hemophilic arthropathy involving mechanical damage, inflammation and metabolic dysregulation underscore the potential of targeting specific pathways, such as iron metabolism, synovial angiogenesis, and cytokine-mediated inflammation, as promising strategies for developing joint-specific therapies in hemophilia care. It is particularly intriguing that, despite our growing understanding of the molecular basis of arthropathy, immunomodulators such as anti-TNF agents and methotrexate—widely regarded as the standard of care for degenerative joint diseases like rheumatoid arthritis, where chronic synovitis is both the cornerstone of joint deterioration and the primary therapeutic target—have not been seriously evaluated for the treatment of hemophilic synovitis [57]. All of these molecules aim to target joint damage and serve as complementary therapies to conventional hemophilia treatment. A recent preclinical study reported promising results with methotrexate in a hemophilia B mouse model, suggesting potential anti-inflammatory benefits in the context of hemophilic arthropathy [58]. Additionally, a clinical case series indicated that anti-TNF-α therapy in people with hemophilic arthropathy led to a reduction in both synovitis and the frequency of hemarthroses, highlighting the potential role of targeted anti-inflammatory treatments in modifying disease progression [59]. As iron deposition is a key driver of synovial inflammation in hemophilic arthropathy, the use of iron chelating agents, such as deferoxamine, might be explored as a potential therapeutic approach to modulate the underlying inflammatory processes [60]. A similar rationale applies to the use of anti-VEGF agents, which inhibit pathological angiogenesis—a process closely linked to chronic synovial proliferation and inflammation in hemophilic arthropathy [61]. By targeting angiogenic pathways, these agents may contribute to reducing synovial vascularization and subsequent rebleeding and joint damage, representing another potential disease-modifying therapeutic strategy.

Synovectomy has been used for many years to treat hypertrophic synovitis in hemophilia patients, especially before the advent of powerful prophylactic therapies that now offer better prevention of bleeding. While surgical synovectomy - whether open or arthroscopic - can reduce breakthrough bleeding, it has significant drawbacks [62]. Open synovectomy is associated with a high risk of joint stiffness and loss of mobility, making postoperative physiotherapy essential to optimize recovery. Early, consistent, and intensive mobilization is essential for minimizing stiffness and optimizing joint function. Radioactive synoviorthesis is a minimally invasive option that effectively reduces pain and bleeding, especially in larger joints. However, its use has been limited by regulatory concerns about radiation exposure and handling [63] although the procedure appears safe and effective [64,65]. Establishing clear guidelines and obtaining necessary approvals are essential to expanding access to RS for the treatment of chronic synovitis in PwH. Additionally, the availability and supply of radioisotopes must be carefully addressed to ensure consistent and effective treatment.

Currently, there are no treatments specifically designed to target synovitis in the pathway to hemophilic arthropathy, despite the widespread use of anti-inflammatory, immunomodulatory, anti-proliferative, and anti-angiogenic agents in other degenerative joint diseases [66]. Synovitis, a hallmark of hemophilic joint disease, plays a critical role in joint damage and pain. However, the standard therapeutic focus remains on preventing bleeding episodes rather than directly targeting the inflammatory processes that are fundamental to synovitis. In conditions such as osteoarthritis and rheumatoid arthritis, these drugs are routinely used to control inflammation, prevent joint degradation and inhibit pathologic vascularization, but they have not yet been integrated into the treatment of hemophilic joint disease. The unique challenge in hemophilia is the need to balance the prevention of bleeding - through clotting factor replacement or other hemostatic treatments - with the desire to modulate the inflammatory response without risk of bleeding complications. This gap in targeted treatment highlights the unmet need for therapies that can specifically target synovitis in pathway to hemophilic arthropathy, providing a dual approach that effectively manages both bleeding and inflammation [67]. The development of such treatments could potentially improve long-term joint health, reduce pain and slow disease progression in hemophilic patients.

3.1. Unmet needs in the management of hemophilia patients with irreversible osteochondral damage

The management of moderate to advanced arthropathic lesions in PwH involves a multifaceted approach aimed at preserving joint function, decreasing pain and improving quality of life. Key aspects include pain management, often with analgesics and anti-inflammatory medications, and physical therapy to help maintain mobility, muscle strength, and joint stability. Intra-articular injections such as corticosteroids, hyaluronic acid, or platelet-rich plasma (PRP) may be used to reduce inflammation, provide lubrication, and promote tissue healing [66]. In cases where conservative treatments fail, major orthopedic surgery, including joint replacement, may be required to restore function and relieve pain. A comprehensive, individualized strategy combining these approaches is essential to optimize outcomes for PwH with irreversible joint damage.

3.2. Pain management

PwH frequently experience joint pain that significantly affects their quality of life and functional ability [68,69]. Beyond physical discomfort, pain also impacts social, psychological, and emotional well-being. Managing hemophilic arthropathy requires addressing both pain and its broader effects on daily life, including beliefs, emotional responses, sleep, mobility, and work. Despite its high prevalence, joint pain remains under-assessed and poorly managed in clinical settings. Physicians should evaluate pain duration and location, as some PwH experience localized joint pain, while others report radiating or widespread discomfort. The International Association for the Study of Pain classifies pain into nociceptive (localized), neuropathic, and nociplastic (widespread) types based on underlying mechanisms. While preliminary evidence supports this classification in PwH [70,71], more advanced diagnostic tools are needed to accurately differentiate between these

pain types. Additional education and training of HCPs caring for PwH is also needed in basic and advanced pain assessment and management skills.

A significant proportion of PwH require pain medication, yet high-quality studies on analgesic use remain scarce. Current evidence is largely based on small studies and expert opinion [72,73]. Pain management typically follows a stepwise approach, starting with paracetamol/acetaminophen and progressing to non-steroidal anti-inflammatory drugs (NSAIDs) and opioids [74,75]. NSAIDs are generally avoided due to their tendency to cause gastrointestinal bleeding and antiplatelet effects, with selective COX-2 inhibitors being preferred [76]. However, in PwH receiving prophylaxis with newer therapies that maintain stable hemostatic levels comparable to mild hemophilia, NSAID use may be considered. Opioids, while sometimes necessary, should be carefully managed to prevent long-term dependence and addiction risks [77]. Alarmingly, recent studies suggest that 56 % of adults with hemophilia use opioids, potentially underestimating actual usage rates. Current guidelines recommend a gradual introduction of opioids, beginning with codeine or tramadol combined with acetaminophen (up to 3–4 times daily). The maximum daily dose of tramadol should not exceed 400 mg, with lower doses advised when used alongside serotonin-norepinephrine reuptake inhibitors to reduce the risk of serotonin syndrome. For advanced chronic hemophilic synovitis, intra-articular dexamethasone may provide temporary pain relief for several weeks especially before surgery [78]. However, further research is needed to optimize pain management strategies in PwH.

Several studies have investigated non-pharmacological approaches to managing pain in PwH [79]. Physiotherapists commonly employ manual techniques such as mobilization or manipulation, which have demonstrated positive effects on pain intensity without increasing bleeding risk. Additionally, exercise has shown potential benefits, although the overall quality of evidence is currently limited. Combining exercise with cognitive-behavioral therapy (CBT) shows promise in enhancing pain management and self-efficacy. While some research suggests that complementary therapies like acupuncture are safe and may alleviate pain, their effectiveness remains inconclusive. A major challenge in managing joint pain in PwH is the absence of clear guidelines regarding the most effective non-pharmacological treatments and their optimal timing of application. The lack of robust experimental evidence and definitive guidelines for assessing and managing pain in PwH highlights a critical need for focused research. Current practices are highly personalized, leveraging interdisciplinary teams to customize treatment approaches. Comprehensive studies evaluating both pharmacological and non-pharmacological interventions for hemophilic arthropathy are essential to enhance joint pain management in PwH.

3.2.1. *Intra-articular therapies for hemophilic arthropathy*

A recent literature review highlighted that intra-articular injections of hyaluronic acid can provide significant relief from joint pain for several months in PwH with advanced hemophilic arthropathy and osteoarthritis. These injections can typically be repeated every 6 to 12 months, depending on patient response and clinical evaluation [80]. Hyaluronic acid, either alone or in combination with corticosteroids, has shown potential as a therapeutic option for managing hemophilic arthropathy-related symptoms [81]. However, the efficacy and safety of alternative therapies, such as intra-articular injections of platelet-rich plasma (PRP) [82], remain less clearly defined in this specific patient population. Current evidence is limited, highlighting the need for more comprehensive studies to assess the therapeutic role of PRP, hyaluronic acid, and corticosteroids within the broader therapeutic arsenal [83]. In addition, innovative therapies, such as LNA043, a derivative of angiopoietin-like 3 (ANGPTL3), might have potential for treating advanced arthropathy in PwH. LNA043 is a potent inducer of chondrogenesis in human mesenchymal stem cells. It promotes cartilage regeneration in preclinical models of osteoarthritis by binding to the integrin α5β1 receptor. In a Phase 1 trial, LNA043 demonstrated good safety and reversed osteoarthritis transcriptome signatures in cartilage. It is now in a Phase 2b trial as a potential disease-modifying treatment for osteoarthritis [84–86]. If current clinical trials in osteoarthritis demonstrate efficacy, further studies could be conducted in patients with hemophilia and advanced arthropathy to evaluate the effectiveness of this promising molecule in treating osteoarthritis associated with hemophilic arthropathy.

3.3. *Physiotherapy: A key component in managing hemophilic arthropathy*

In patients with active synovitis, physiotherapy—particularly supervised low-load joint mobilization—is essential. Once bleeding is controlled, rehabilitation should begin promptly, following the POLICE principle (Protection, Optimal Loading, Ice, Compression, Elevation), which favors early controlled loading over prolonged rest to avoid complications from immobilization. When initiated safely after acute pain subsides and with clotting factor support, gentle exercises can significantly improve joint function. Clinical evidence supports the safety and efficacy of early mobilization in hemophilia, demonstrating benefits in restoring flexibility, strength, and coordination [87]. Early intervention may also reverse synovial inflammation and prevent progression to chronic arthropathy. Regular physical therapy enhances mobility, reduces pain, strengthens periarticular muscles, and stabilizes joints, thereby lowering the risk of re-bleeding. However, standardized protocols for joint mobilization and rehabilitation strategies remain to be clearly defined.

Physiotherapy plays a key role in managing musculoskeletal problems and enhancing mobility in PwH, yet challenges remain in evidence-based practice, acute care, and the absence of clear guidelines. Despite advancements, gaps persist in accessibility, standardization, and individualized strategies. In hemophilia treatment centers (HTCs), physiotherapists are often underused, with a focus on acute rather than preventive or long-term care, and only 30 % of European centers consistently provide physiotherapy, with variable service quality [88]. The lack of strong clinical evidence and standardized protocols continues to limit optimal care for hemophilic arthropathy. Addressing these shortcomings is essential to improve joint outcomes, prevent complications, and support a better quality of life for PwH, highlighting the need for further research and clearer guidance.

Self-physiotherapy programs provide effective solutions to accessibility challenges, especially in low-resource settings, by enabling PwH to manage their musculoskeletal health independently and reduce dependence on physiotherapists. In low-income countries, community-based initiatives—such as one in Côte d'Ivoire—have shown success, with culturally adapted exercise and education programs improving joint function, strength, and range of motion, and achieving high adherence and satisfaction [89]. In high-income settings, hybrid models like the e-Exercise Hemophilic Arthropathy program combine in-person sessions with app-based support. While well-received and effective at reducing activity limitations, its impact on pain and physical activity remains modest, suggesting the need for refinement [90]. These adaptable self-management models demonstrate potential to enhance autonomy and quality of life for PwH. Additionally, physiotherapists and adapted physical activity instructors play a crucial role in preventing joint damage. Physical activity helps strengthen muscles, improve coordination and balance, and reduce the risk of injury—especially in younger PwH—while personalized programs for those with joint damage can slow disease progression and alleviate symptoms [91]. Patient-level barriers, including pain and frailty, can be addressed through tailored, patient-centered exercise programs. Empowering PwH with the knowledge and autonomy to manage their own exercise is essential, especially for older PwH who require gradual, structured programs to maintain health and functionality [92,93].

Orthotic interventions like splints, braces, and foot orthoses are commonly used in PwH to reduce joint strain, but strong evidence from

controlled trials is lacking. While small studies suggest benefits—especially for ankle arthropathy—there is no consensus on the most effective devices. Some recommend insoles for moderate cases and orthopedic shoes for severe ones [94]. Despite existing guidelines for ankle arthropathy, specific recommendations on orthotic use in hemophilia are missing, highlighting the need for personalized, multidisciplinary care.

Improving physiotherapy access for PwH requires better education, as many physiotherapists lack hemophilia-specific training. Rare disorders are often overlooked in current programs, creating a knowledge gap. Targeted, on-site training and mentoring by specialized physiotherapists are more effective than sending trainees to developed countries, where they may not encounter severe cases. This approach benefits both learners and trainers. Patient education is also vital—personalized plans and goal-setting can improve adherence and clinical outcomes.

Barriers to physiotherapy accessibility for PwH include financial and geographical challenges. Inadequate reimbursement and high costs limit access, especially in rural areas with few qualified physiotherapists. Addressing these barriers requires targeting both economic and political factors, as well as promoting education and the adoption of solutions like self-physiotherapy and technology-based interventions to improve care availability and effectiveness.

3.4. Major orthopedic surgery in hemophilic arthropathy: Current approaches and unmet needs

Orthopedic interventions are essential for managing hemophilic arthropathy, especially in advanced stages of joint damage, yet gaps in access, standardization, and application persist. Procedures like synovectomy, joint aspiration, and arthroplasty are usual for controlling inflammation, relieving pain, and preserving mobility, but the absence of clear guidelines hinders their optimal use. Synovectomy (surgical, radioactive or chemical) effectively reduces inflammation and preserves joint function, while radiological synoviorthesis offers a minimally invasive option for chronic synovitis. However, access to these treatments is limited, especially in low- and middle-income countries due to a lack of expertise and infrastructure, resulting in underutilization [95,96]. Gaps in clinician awareness also hinder adoption, delaying interventions and worsening disease progression. Improving access, education, and standardized guidelines is crucial to optimizing outcomes. In resource-limited settings, chemical synovectomy with rifampin or corticosteroids offers a lower-efficacy alternative, but expanding research and use of these options could help bridge the gap.

Angiographic embolization may be considered a promising therapeutic option—and a coagulation factor-sparing strategy—for managing joint bleeds that are refractory to replacement therapy. Its potential efficacy is thought to stem from targeting pathologic reactive angiogenesis associated with chronic synovitis. However, it is important to note that despite its effectiveness, arterial embolization remains an invasive procedure, with complication rates reported as high as 25 % [97,98]. Joint aspiration can relieve symptoms of acute hemarthrosis, with some studies suggesting potential short- and long-term benefits [99–101]. However, its impact on recovery is unclear. The lack of clear guidelines adds to uncertainty, and further research is needed to assess its safety, efficacy, and long-term benefits.

A key unmet need in orthopedic care is elbow arthropathy, which often receives less orthopedic care than other joints, even in high-income countries. In early stages, synovectomy is the preferred treatment for chronic synovitis with minimal cartilage damage, while radial head excision can relieve pain and improve forearm rotation in cases of joint degeneration. However, synovectomy alone offers limited mobility improvements, highlighting the need for adjunct therapies. In advanced stages, total elbow arthroplasty can reduce pain and restore function, but its high complication risk and shorter prosthetic survival limit its use. Compared to hip and knee arthroplasties, elbow prosthesis shows poorer outcomes [102,103], emphasizing the need for alternative surgical solutions to better address advanced joint damage.

4. Conclusions and future perspectives

Recent advances in hemophilia treatments, including long-acting factor products, non-factor therapies, and gene therapy, have reduced bleeding episodes and improved joint health, enabling PwH to engage in daily life activities and physical activity with less risk of bleeding. However, their long-term effects on joint health and physical activity remain unclear, highlighting the need for reliable methods to assess activity levels.

While annual bleeding rates (ABRs) have traditionally measured treatment efficacy, they fail to capture early joint changes, particularly in adults treated since childhood. Guidelines from the WFH and the International Classification of Functioning, Disability, and Health (ICF) emphasize comprehensive health assessments, but lack of sensitive tools hinders their implementation.

Despite progress, critical gaps persist in understanding hemophilic arthropathy, in pain management strategies, where treatment approaches are often extrapolated from other conditions rather than tailored to hemophilia-specific pathology and in treatments targeting synovitis. Addressing these gaps requires dedicated clinical trials focused on pain relief, synovial hypertrophy, and advancements in imaging and biomarker research. Strengthening collaboration between researchers and clinicians is essential to developing targeted interventions that better meet the unique needs of this patient population.

Practice points

- Early and long-term prophylaxis remains the most effective means of preventing hemophilic arthropathy.
- While joint ultrasound has enhanced the diagnosis of synovitis, it is not available in all hemophilia centers, and the early detection of joint involvement continues to be an unmet need as of 2025.
- In hemophilia centers, physiotherapists' roles have traditionally focused on managing arthropathy; however, there is a growing need to further develop personalized prevention programs that include tailored physical activity and psychological support.
- Additionally, the management of pain associated with hemophilic arthropathy is often inadequately addressed, highlighting the need for better awareness among hematologists regarding both pharmacological treatments and non-pharmacological techniques.

Research agenda

- Identification of Novel Biomarkers for Early Diagnosis and Monitoring of Joint Damage
- Targeted Joint Treatments for Hemophilic Arthropathy
- Accurate and Standardized Tools for Measuring Physical Activity
- Advancement of Orthotic Interventions
- Improved Pain Management Strategies

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