REVIEW ARTICLE

Mechanisms of blood-induced joint disease in hemophilia and potential novel targets for interventions

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Abstract

Hemophilic joint disease, or blood-induced joint disease (BIJD), arises from recurrent or even subclinical hemarthroses that initiate a cascade of iron-driven synovial and cartilage pathology. When blood enters the joint, iron deposition triggers oxidative stress, generating IL-1β- and TNF-α–mediated inflammation, synovial hyperplasia, and persistent angiogenesis. Foundational studies show that iron exposure activates oncogene-like programs in synovial fibroblasts, including c-myc and MDM2, promoting proliferative and anti-apoptotic behavior that contributes to villous hypertrophy. Contemporary single-cell analyses reveal heterogeneous fibroblast, endothelial, and mast cell populations that orchestrate iron handling, inflammation, and vascular remodeling. Notably, endothelial cells exposed to repeated bleeding exhibit ferroptosis signatures, increased permeability, and signaling through ferritin light chain to SCARA5-positive fibroblasts, forming an iron-responsive stromal circuit that may predispose joints to rebleeding. Macrophages propagate osteochondral injury through iRhom2/ADAM17-dependent TNF-α shedding, linking hemarthrosis to bone loss. Cartilage injury occurs rapidly: even short exposures to low concentrations of blood induce irreversible chondrocyte apoptosis, reduced proteoglycan synthesis, and matrix degradation driven by reactive oxygen species and iron. Recent discoveries identify TNXB–AKT signaling as a critical cartilage-protective pathway lost in hemophilic arthropathy. Despite advances in systemic and non-factor therapies, joint bleeding and arthropathy persist, highlighting the need for mechanism-based interventions beyond hemostasis. Potential targets include iron/reactive oxygen species modulation, endothelial ferroptosis inhibition, mast-cell stabilization, TNF-α pathway blockade, fibroblast state reprogramming, and activation of AKT-mediated cartilage survival pathways. An integrated model positions hemarthrosis as the initiating event and iron-centered inflammatory amplification as the driver of chronic joint degeneration, underscoring opportunities for joint-directed therapeutic innovation.

Introduction

Hemophilia is an inherited bleeding disorder due to deficiency of the action of coagulation factor (F)VIII (FVIII) or FIX activity.[1] Bleeding into joints (hemarthrosis) is the cardinal manifestation and the trigger for the development of hemophilic arthropathy. Despite decades of progress in the development of therapeutics to treat and prevent bleeding,[2,3] joint bleeding persists and its complications remain a major cause of morbidity in people with hemophilia.[4] Dargaud *et al.* outlined the persistent gaps in the diagnosis and management of hemophilic arthropathy including incomplete bleed prevention, uncertain long-term joint outcomes of novel therapies, limited tools for early/subclinical damage, inadequate pain strategies, and the lack of interventions that specifically target synovium or cartilage. Among the processes that are thought to lead to hemophilic arthropathy (Figure 1A)[5-11] are iron-triggered: (i) oxidative stress leading to interleukin (IL)-1β and tumor necrosis factor (TNF)α-mediated inflammation;[12,13] (ii) angiogenesis and increased vascular permeability;[14-17] and (iii) chondrocyte apoptosis and suppressed matrix synthesis (Figure 1B).[18,19] Here, we discuss these biological processes that lead to blood-induced joint disease (BIJD) in people with hemophilia and the potential direct interventions that might be explored to address BIJD in people with hemophilia. We provide the reader with a review of historical and modern data on the pathobiology of this disorder and synthesize this information into a conceptualized, multi-system cascade of events involving multiple cell types and signaling pathways impacted by iron.

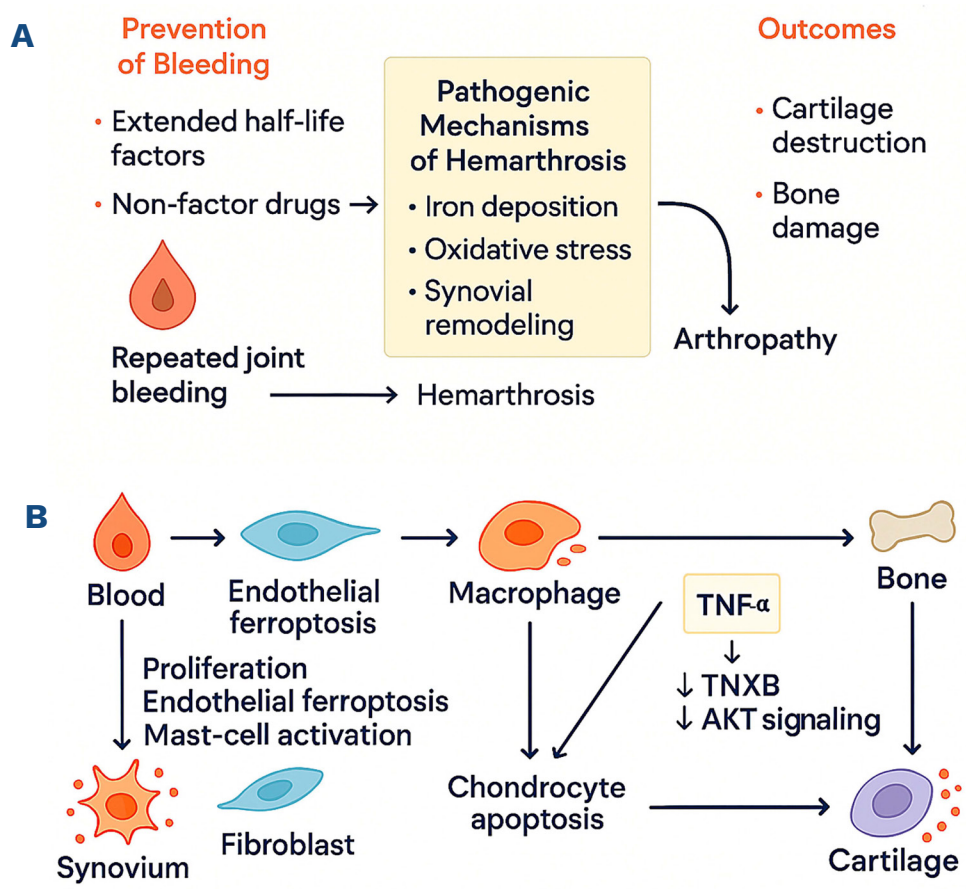

Figure 1. Blood-initiated mechanisms underlying hemophilic arthropathy. (A) Schematic overview of blood-initiated joint disease in hemophilia. Recurrent joint bleeding (hemarthrosis) triggers a cascade of pathogenic processes that extend beyond the acute bleeding event and are incompletely prevented by contemporary hemostatic therapies, including extended half-life clotting factors and non-factor agents. Intra-articular blood exposure leads to iron deposition, oxidative stress, and synovial remodeling, creating a pro-inflammatory microenvironment within the joint. These interrelated mechanisms promote progressive synovitis and drive downstream structural damage. Over time, persistent inflammatory and catabolic signaling culminates in the characteristic outcomes of hemophilic arthropathy, including fibrotic synovium, cartilage destruction, bone damage, and irreversible joint dysfunction. (B) Cellular and molecular mechanisms contributing to the progression of hemophilic arthropathy. Blood exposure within the joint initiates endothelial injury and ferroptosis, accompanied by synovial proliferation and mast-cell activation. Activated macrophages (both tissue resident type A synovial cells and blood-derived monocytes/macrophages) serve as central amplifiers of inflammation, producing cytokines, such as tumor necrosis factor, which disrupt homeostatic signaling pathways, including AKT-dependent survival pathways, and downregulate extracellular matrix–stabilizing components. Crosstalk between macrophages, fibroblasts, endothelial cells, and chondrocytes accelerates chondrocyte apoptosis and matrix degradation, ultimately leading to cartilage loss. Parallel effects on subchondral bone contribute to skeletal damage. Together, these interconnected vascular, inflammatory, and degenerative pathways explain how hemarthrosis evolves into chronic hemophilic arthropathy despite effective control of overt bleeding. AKT: protein kinase B; TNF-α: tumor necrosis factor alpha; TNXB: tenascin X.

Hemarthrosis as the inciting event: blood and iron set the stage for blood-induced joint disease

Blood entering the closed synovial space initiates synovitis and sets up a feed-forward loop involving iron deposition, oxidative stress, and proliferative synovial remodeling that ultimately destroys cartilage and bone. The seminal review by Valentino[5] framed BIJD as a blood-initiated disease in which iron/heme and other blood components are central drivers of inflammation, synovial hyperplasia, and degenerative change, establishing a conceptual throughline still used today. In contemporary updates, reviews reiterate that even subclinical hemarthroses can lead to arthropathy[6] and that prevention of bleeding through novel extended half-life FVIII or FIX products and non-factor drugs[3,4,20] has not eliminated joint disease, emphasizing the need to target intra-articular pathogenic mechanisms downstream of bleeding.[21]

A robust experimental foundation underpins these concepts. A murine model of FVIII deficiency created by Valentino and colleagues recapitulated human hemophilic synovitis and enabled mechanistic dissection. Repeated or single induced bleeds produced synoviocyte hypertrophy/hyperplasia, neovascular responses, hemosiderin deposition, and progressive cartilage/bone changes mirroring human pathology and providing a platform for testing interventions.[22,23] Together, these models situate blood as the instigator and iron-laden synovium as the biological “reactor” that converts bleeding events into chronic joint pathology.

Two additional lines of evidence underscore the primacy of blood as the driver. First, localized intra-articular replacement of the deficient factor (e.g., FIX) prevents synovitis in hemophilia B mice even in the absence of detectable circulating FIX, demonstrating that joint-directed control of bleeding can interrupt BIJD at its source.[24] Second, aspiration or rapid clearance of blood from the joint is mechanistically rational:

in vitro and *in vivo* work shows that even brief exposures of cartilage to blood can initiate persistent metabolic injury, while thresholds of concentration (≥10% v/v) and duration (≥2 days) are sufficient to produce irreversible alterations in chondrocyte function.[19,25]

The key pathobiological themes are that iron deposition leads to oxidative stress which, in turn, causes synovial proliferation.

Iron is a molecular linchpin, it accumulates as hemosiderin, catalyzes reactive oxygen species (ROS), and reprograms synovial and cartilage cells toward proliferative and apoptotic fates.[26-30] We next review how iron and other blood-derived signals engage specific synovial and joint resident cell types to propagate BIJD.

Synovial lining and fibroblasts: iron oncogene signaling, heterogeneity, and crosstalk

Iron drives oncogene programs and synovial hyperplasia

Pioneering studies showed that iron can directly induce proliferation of human synovial fibroblasts and activate proto-oncogenic pathways.[22,31] *In vitro*, ferric iron (ferric citrate) increases c-myc expression and increases growth of primary human synovial fibroblasts, effects that could be reversed by the pro-apoptotic sphingolipid ceramide.[31] This work linked iron to c-myc–dependent growth control, proposing a tumor-like proliferative phenotype of hemophilic synovium. Extending these observations, hemarthrosis *in vivo* and iron *in vitro* upregulated MDM2, a p53 binding protein, in synovium. Iron exposure caused an ~8-fold rise in MDM2 expression in normal human synovial cells.[22] MDM2 upregulation provides a mechanistic path to anti-apoptosis and synovial overgrowth, aligning with histological villous hypertrophy observed after bleeds.

These oncogene-like changes are not merely cell culture artifacts. In a murine model of hemophilia A, a single hemarthrosis induces villus formation, synovial hyperplasia, and angiogenesis, with a strong correlation between synovial and vascular hyperplasia, underscoring the angiogenic dependency of expanding inflamed synovium.[22] Reinforcing the model's fidelity, the histological grading system emphasizes vascularity and hemosiderin discoloration as hallmarks of iron-driven synovitis.[32]

Synovial fibroblast states and pathogenic specialization

Contemporary single-cell and spatial analyses in inflammatory arthritis have redefined the "fibroblast" as a family of phenotypically and functionally distinct states, varying by location (lining *vs*. sub-lining), epigenetic imprinting, and microenvironmental cues. While this work was pioneered in rheumatoid arthritis (RA), it provides a conceptual scaffold to interpret synovial fibroblast heterogeneity in hemophilia. Machado & Firestein summarized at least four fibroblast states in RA with distinct effector repertoires, some catabolic/invasive, others chemokine-rich and emphasized their plasticity under cytokine/growth factor influence.[33] Such a framework is directly relevant to BIJD, in which repeated exposure to blood and iron could skew fibroblast states toward angiogenic, matrix-degrading, or iron-handling phenotypes.

Recent single-cell RNA sequencing of hemophilic synovium by Lin *et al*. validated this idea in the context of hemophilia.[34] They showed that following exposure to iron and activation of heme oxygenase (HMOX), endothelial cells can induce scavenger receptor class A 5 (SCARA5) fibroblast subpopulations by interacting with the ferritin light chain (FTL) from stressed endothelium which appears linked to ferroptosis responses in the synovial niche (Figure 2). This iron-handling fibroblast state situates iron metabolism within stromal crosstalk, extending classic iron-oncogene observations into a microenvironmental circuit.

Insights from osteoarthritis (OA) single-cell atlases further illustrate fibroblast functional bifurcation: fibroblasts positive for cartilage intermediate layer protein (CILP) associate with non-damaged chondrocytes and exhibit reparative transcriptomes, whereas fibroblasts expressing periostin/osteoblast-specific factor (POSTN) interact with damaged chondrocytes and display catabolic/inflammatory signatures.[35] These programs suggest that stromal context and crosstalk with cartilage drive fibroblast specialization toward protective *versus* injurious roles – templates that plausibly translate to hemophilic synovium under iron and bleed stress.

To summarize, iron skews synovial fibroblasts toward proliferation (c-myc/MDM2) and, through vascular and endothelial signals, toward iron removal (SCARA5) states, the balance of which can influence cartilage health and outcomes.

Synovial macrophages and a cytokine axis: TNF-α, ADAM17/iRhom2, and osteo-immune crosstalk

Macrophages are pivotal in translating blood-borne iron and damage signals into cytokine milieus that remodel bone and cartilage.[36] In a murine study, blood or its components triggered inactive rhomboid 2 (iRhom2)/a disintegrin and metalloproteinase domain-containing protein (ADAM)17-dependent shedding of TNF-α from macrophages; genetic or pharmacological disruption of TNF-α or iRhom2 reduced osteopenia and synovitis after induced hemarthrosis in FVIII-deficient mice.[37] This defines a blood → macrophage → TNF-α axis as a core pathway of blood-induced bone loss and synovial inflammation in hemophilic arthropathy. The mechanistic chain links blood exposure to TNF-alpha convertase enzyme (TACE) or ADAM17 activity and TNF-α

release, providing actionable targets for protecting peri-articular bone.

Beyond TNF-α, broader cytokine networks (IL-1β, IL-6, chemokines) contribute to BIJD, as reviewed comprehensively by Wojdasiewicz *et al*.[38] Blood-derived iron and cell debris amplify innate immune activation, while synovial lining cells perpetuate matrix metalloproteinase production and angiogenesis reinforcing a pro-inflammatory synovial ecosystem. Clinical pathological reviews further connect these cytokine circuits with chronic pain and structural decline, underscoring unmet needs in mechanism-directed therapies beyond hemostasis.[39]

To summarize, targeting TNF-α processing (iRhom2/ADAM17) and associated cytokine nodes early after bleeding may interrupt bone catabolism and synovial inflammation after bleeds, complementing factor prophylaxis.[40]

Endothelial cells and mast cells: vascular damage, ferroptosis, and permeability phenotypes

Vascular elements are central actors in BIJD. Histological and morphometric data show that synovial hyperplasia tightly correlates with vascular expansion,[41] implying that progression depends on endothelial proliferation and nutrient supply. Single-cell data now add mechanistic depth. Lin *et al*. demonstrated that repeated bleeding fosters iron deposition and a ferroptosis signature in synovial endothelium, including an HMOX1⁺ endothelial disposition indicative of oxidative stress and heme catabolism.[34] Endothelial ferroptosis is postulated to injure microvasculature and drive endothelial migration, altering permeability[42,43] and potentially predisposing to re-bleeding.[44,45]

It is recognized that iron accumulation from hemarthroses drives synovitis and cartilage damage in hemophilic arthropathy. Ferroptosis has been experimentally demonstrated as a key mechanism of chondrocyte death under iron-rich conditions, including models of hemophilic arthropathy, in which inhibition of ferroptosis attenuates cartilage damage.[46,47] Preclinical studies show that D-penicillamine and deferoxamine reduce synovial iron and inflammation, while clinical experience with iron chelators confirms effective depletion of systemic iron but not of the iron within synovial tissues. Translational studies highlight that timing and joint delivery are critical, as on-demand chelation has not yet demonstrated disease modification.[48] Testing of agents that reduce lipid ROS accumulation such as the ferroptosis inhibitors ferrostatin 1 and liproxstatin 1 should be undertaken.[46,49]

Endothelial–fibroblast crosstalk links vascular stress to stromal reprogramming.[50,51] Iron-stressed endothelial cells signal via FTL to SCARA5 on fibroblasts, promoting a SCARA5⁺ fibroblast subset with iron-handling features; this circuit connects iron biology to stromal heterogeneity and potential matrix outcomes.[34] The FTL to SCARA5 endothelial-to-fibroblast circuit is a direct mechanistic link between iron biology and stromal remodeling that may be operative in hemophilic arthropathy (Figure 2).

The pro-inflammatory milieu following bleeding results in iron retention and disturbed lymphangiogenesis.[52] The findings of von Drygalski's laboratory suggest a link between iron homeostasis and lymphangiogenesis.[52,53] Intact lymphatics are necessary for the removal of iron-laden macrophages, a process that is dependent on FVIII. In the absence of FVIII, vascular changes including expression of α-smooth muscle actin (SMA), endoglin (CD105) and vascular endothelial growth factor (VEGF) result in changes in vascular remodeling and in joint perfusion.[44] In FVIII-deficient mice, hemarthrosis provokes defective lymphangiogenesis, synovial

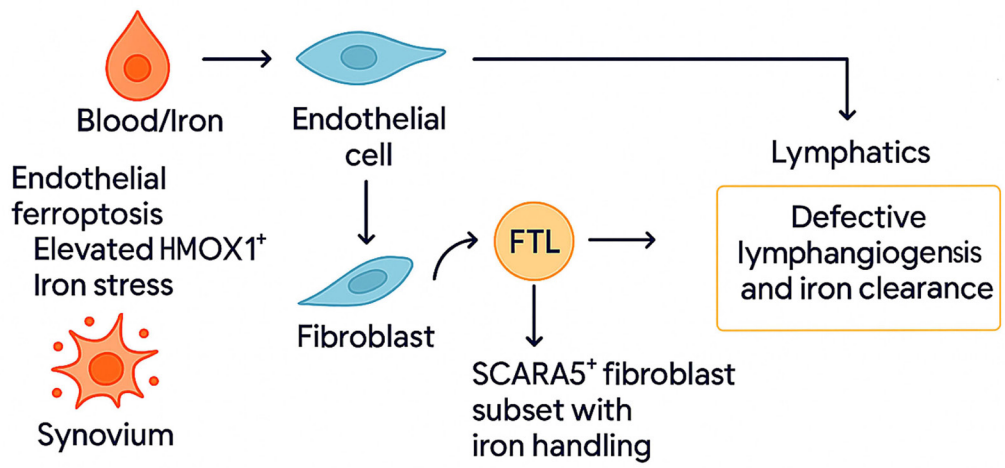

Figure 2. Iron-driven mechanisms of synovial remodeling in hemophilic arthropathy. Schematic representation of pathways linking intra-articular blood and iron exposure to chronic synovial remodeling. Hemarthrosis results in iron accumulation, triggering endothelial cell injury and ferroptosis, accompanied by induction of iron-responsive stress pathways, including HMOX1. Endothelial dysfunction and altered fibroblast phenotypes promote synovial expansion and remodeling. A distinct SCARA5⁺ fibroblast subset contributes to intracellular iron handling and ferritin light chain accumulation. Concurrently, impaired lymphangiogenesis limits iron clearance from the joint, reinforcing local iron toxicity and inflammation. Together, these processes perpetuate synovial pathology and drive progression of hemophilic arthropathy. FTL: ferritin light chain; HMOX1: heme oxygenase 1; SCARA5: scavenger receptor class A 5.

iron retention, and iron-laden macrophages, effects which can be mitigated by therapeutic FVIII to restore lymphatic remodeling, accelerate iron clearance, and improve cartilage health. These dynamics parallel single-cell evidence of HMOX1⁺ endothelial ferroptosis and FTL→SCARA5 signaling inducing SCARA5⁺ fibroblasts in hemophilic arthropathy, connecting iron handling to stromal remodeling and outcomes in hemophilic arthropathy.

A further link to the importance of endothelial cells is activated protein C (APC), which is generated when thrombin binds thrombomodulin on endothelial cells. APC is classically considered an anticoagulant (it inactivates factors Va and VIIIa). Following acute hemarthrosis, APC binds to the endothelial protein C receptor to exert a protective effect through protease activated receptor 1 signaling, stabilizing endothelial barriers and reducing vascular permeability. Importantly, APC reduces leukocyte adhesion and also functions as an inflammatory modulator inhibiting nuclear factor kappa B (NF-κB) activation to reduce the synthesis of TNF-α, IL-1β and IL-6. These anti-inflammatory effects are easily overwhelmed by repeated bleeding and dysregulated APC activates matrix metalloproteinases to degrade collagen. Inhibition of APC activity increases the permeability and fragility of synovial endothelial cells, thus increasing the propensity to re-bleeding. APC therefore emerges at the intersection of inflammation, endothelial biology, and synovial remodeling.

An unexpected and disease-defining finding in hemophilic synovium is the presence of activated perivascular mast cells, more prominent than in OA or RA comparators. Lin *et al*. identified activated mast cells as a distinctive immune population in hemophilic arthropathy, suggesting roles in vascular permeability, bleeding propensity, and early inflammatory amplification.[34] Heme iron activates mast cells, to release algogenic and pruritogenic mediators, and neutrophils, inducing the formation of extracellular traps, nano tubes and extracellular vesicles in addition to the secretion of proteases.[46,47] Candidate mediators released by mastcells include tryptases (e.g., TPSB2), consistent with mast-cell effects on endothelial junctions and matrix.[48,49] The enrichment of activated perivascular mast cells, which may establish a paracrine mast-cell–angiopoietin (ANGPT)-2 axis whereby mast-cell–derived mediators (such as TNF-α, IL-1β, IL-6, various proteases, and VEGF) activate the endothelium, inducing ANGPT-2 upregulation; in this inflammatory milieu,[50] ANGPT-2 – an endothelial-derived regulator of the ANGPT/Tie-2 pathway that antagonizes ANGPT-1 while synergizing with VEGF – might thereby act as a central driver of angiogenesis and neovessel formation in hemophilic arthropathy.[51] Inhibition of mast-cell function is being used in a variety of diseases and Worrall and Reber provide an excellent summary of mast-cell-targeted therapies.[52]

The implications of the foregoing are that a mast cell–endothelium axis may modulate vascular leakage and inflammatory tone, while endothelial ferroptosis and FTL–SCARA5 signaling organizes stromal iron responses, suggesting novel targets (e.g., ferroptosis regulators, mast-cell mediators) to limit re-bleeding and synovitis.

Chondrocytes and cartilage matrix: apoptosis, AKT/TNXB signaling, and toxicity of iron-reactive oxygen species

Direct effects of blood on cartilage viability and matrix

A pivotal observation is that cartilage damage can occur independent of overt synovitis with even short exposures to blood: human cartilage co-cultured with 50% blood (or red blood cells with mononuclear cells) shows profound, durable inhibition of proteoglycan synthesis and tripling of apoptotic chondrocytes; caspase inhibitors partially rescue synthetic activity, linking apoptosis to functional decline.[19,25] Mechanistically, oxidative stress mediates these effects: ROS scavengers and antioxidant interventions attenuate blood-induced injury, and iron from red blood cells catalyzes reactive species that damage chondrocytes. Threshold studies demonstrate that 2 days of exposure to 10% (v/v) blood suffices to cause prolonged damage *in vitro*, with poor reversibility, data often cited to support rapid treatment of hemarthrosis and/or evacuation of hemarthrosis.

Epigenetic signaling in cartilage in hemophilic arthropathy: TNXB → AKT → chondroprotection

Contemporary human/mouse translational work has identified tenascin-XB (TNXB) as a cartilage-centric regulator of BIJD. TNXB organizes and maintains tissue structure by regulating the production and assembly of certain types of collagens and its deficiency is a cause of Ehlers-Danlos syndrome.[54] Chen *et al*. found aberrant DNA methylation and downregulation of TNXB in cartilage in cases of hemophilic arthropathy; TNXB deficiency in FVIII-deficient mice promotes matrix degradation, subchondral bone loss, and chondrocyte apoptosis.[18] Mechanistically, TNXB loss suppresses phosphorylation of AKT (a protein whose name is derived from thymoma tissue isolated from the AK mouse strain, also known as protein kinase B), and AKT supplementation rescues chondrocyte survival and matrix integrity, suggesting that the TNXB–AKT axis acts as a therapeutic lever in cartilage degeneration in hemophilic arthropathy (Figure 2A). These findings build on the older BIJD paradigm[55] by placing a specific extracellular matrix gene and survival pathway at the center of blood-induced cartilage injury, linking epigenetics of hemophilic arthropathy cartilage to signal transduction vulnerability under iron/ROS stress.

The implications of these observations are that blood exposure triggers chondrocyte apoptosis and diminishes matrix synthesis through ROS/iron injury and TNXB downregulation further reduces AKT survival signaling, compounding matrix loss (Figure 3A). Activation of the AKT pathway is chondroprotective in preclinical systems and may be a target for

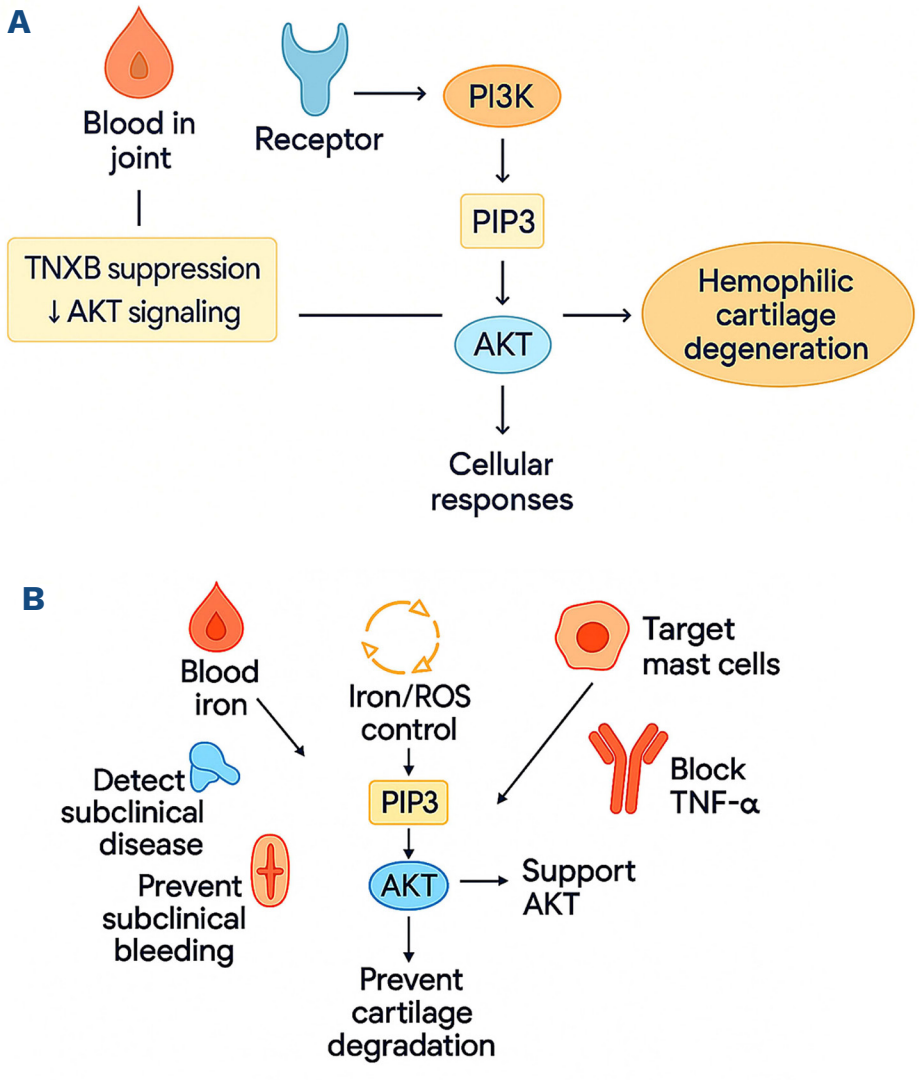

Figure 3. Disruption and therapeutic modulation of PI3K–AKT signaling in hemophilic cartilage degeneration. (A) Schematic representation of PI3K–AKT pathway dysregulation following intra-articular bleeding. Blood exposure within the joint alters receptor-mediated signaling and is associated with suppression of TNXB, a matrix protein implicated in cartilage integrity. Reduced TNXB expression leads to impaired activation of the PI3K–AKT axis, characterized by diminished phosphatidylinositol 3 phosphate (PIP3) generation and downstream AKT signaling. Attenuation of AKT-dependent cellular responses compromises chondrocyte survival, stress resilience, and matrix homeostasis, thereby promoting hemophilia-associated cartilage degeneration. (B) Conceptual framework highlighting diagnostic and therapeutic opportunities to preserve cartilage in hemophilia by restoring or supporting AKT signaling. Potential interventions include improved prevention and detection of subclinical joint bleeding, control of iron-mediated oxidative stress, targeting of mast-cell–mediated inflammation, and blockade of pro-inflammatory cytokines such as tumor necrosis factor α and supporting AKT signaling to protect and preserve cartilage. Early detection of subclinical joint disease using sensitive imaging or biomarkers may enable timely intervention. Strategies aimed at supporting PI3K–AKT signaling are proposed to counteract chondrocyte apoptosis and matrix degradation, complementing hemostatic therapy and addressing non-hemostatic drivers of hemophilic arthropathy. AKT: protein kinase B; PI3K: phosphatidylinositol 3-kinase; PIP3: phosphatidylinositol 3 phosphate; ROS: reactive oxygen species; TNF-α: tumor necrosis factor alpha; TNXB: tenascin XB.

intervention clinically. Multiple intervention points may mitigate hemophilic cartilage degeneration (Figure 3B). Following joint bleeding, rapid removal of intra-articular blood[56,57] or joint-targeted hemostasis[24] to reduce iron exposure and synovial activation have been proposed. Targeting iron-driven oxidative injury, endothelial ferroptosis, and mast-cell–mediated vascular permeability may interrupt upstream inflammatory amplification thereby being beneficial. Enhancing FVIII availability to restore lymphangiogenesis and accelerate iron clearance may improve post-bleed recovery and reduce the likelihood of re-bleeding. Blockade of iRhom2/ADAM17-dependent TNF-α release may further limit synovial and osteochondral damage. Finally, preserving TNXB expression or augmenting AKT signaling provides direct chondroprotection against apoptosis and matrix loss. Imaging-based detection of subclinical bleeding may enable timely intervention; however, the minimum exposure time to trigger pathology is not known and therefore prevention of bleeding[6] and chondroprotective prophylaxis are the optimal interventions.

Preventing bleeding alone is necessary but insufficient; true chondroprotection requires modifying intra-articular biological responses to blood, iron, synovial inflammation, and cartilage-intrinsic stress. Physiological compression activates the integrin-phosphatidylinositol 3-kinase (PI3K)-AKT signaling pathway providing protective signals to cartilage but, conversely, abnormal loading following joint bleeding inhibits PI3K and mitigates these protective pathways, suggesting rest and limited weight-bearing are necessary following joint bleeding.[20,58,59]

Chondroprotective prophylaxis can be accomplished in several ways. All are predicated on the activation of PI3K which is central to this mechanism (Figure 3B). PI3K is activated when its regulatory subunit (p85) binds phosphotyrosine motifs or when its catalytic subunit (p110) is engaged by upstream membrane signals. Therefore, PI3K can be activated by supplying the ligands to one of its receptor tyrosine kinases including insulin-like growth factor-1 receptor, insulin receptor, platelet-derived growth factor receptor, epidermal growth factor receptor, VEGF receptors 1/2, or fibroblast growth factor receptors, by activation of chemokine-linked G protein–coupled receptors, by initiation of the JAK/STAT signaling pathway following ligation of the IL-2, IL-4, IL-6 family receptors or the TNF family of receptors, or following engagement of integrins activating the focal adhesion kinase-Src pathway.

Bone and osteochondral unit: the TNF-α pathway and structural consequences

Peri-articular bone is not spared in BIJD. In FVIII-deficient mice, bleeding triggers osteopenia adjacent to the affected

joint. Mechanistically, blood components activate macrophage iRhom2/ADAM17, increasing TNF-α in the joint; blocking TNF-α or iRhom2 mitigates both synovitis and bone loss. This situates TNF-α, processed by ADAM17, at the nexus of osteo-immune damage after bleeding and offers path-specific targets to preserve bone architecture in hemophilic arthropathy.[37]

Clinically, arthropathy remains prevalent despite hemostatic advances,[3,4,20] reinforcing the need to address post-hemorrhagic biological cascades in the osteochondral unit. Reviews highlight persistent joint remodeling, pain, and eventual joint replacement in some patients,[21] calling for mechanism-based adjuncts (anti-cytokine strategies, antioxidants, ferroptosis modulators, synovial targeted approaches) alongside prophylaxis.[4]

An integrative model: from blood to multi-cellular pathology

Bringing together classic and modern data, BIJD can be conceptualized as a multi-system cascade (Figure 4): (i) hemarthrosis introduces blood/iron into the joint; (ii) synovial iron loading drives ROS and proliferative/anti-apoptotic programs (c-myc, MDM2), promoting hyperplasia and angiogenesis; vascular expansion supports ongoing synovial growth; (iii) endothelial cells undergo ferroptosis-like stress ($HMOX1^+$ states), altering permeability and favoring re-bleeding; mast cells amplify vascular leak and inflammation; (iv) endothelial–fibroblast FTL→SCARA5 signaling induces a $SCARA5^+$ fibroblast subset, embedding iron-handling within stromal crosstalk; (v) macrophages exposed to blood signal via iRhom2/ADAM17 to shed TNF-α, propagating synovitis and bone resorption; and (vi) chondrocytes suffer apoptosis and matrix synthetic failure from direct blood/iron/ROS exposure; TNXB epigenetic loss disables AKT survival signaling, accelerating extracellular matrix degradation; and AKT activation is protective.

This integrated view reconciles historical "chemical injury" models with an immune vascular stromal network identified by single-cell genomics and highlights therapeutic nodes beyond mere hemostasis.

Therapeutic implications and disease modification

Hemostasis remains foundational, but site-directed strategies matter

Prophylaxis and prompt control of bleeding are indispensable for preventing the initiating insult, blood and iron. Yet elegant experiments show that intra-articular factor delivery (protein or AAV-mediated) can suppress synovitis even without systemic factor, underscoring the joint-autonomous nature of BIJD and supporting local or joint-targeted adjuncts. Reviews emphasize that despite non-factor therapies and extended half-life products, arthropathy persists in subsets, motivating mechanistic adjuvants.

Mechanism-informed adjuncts

Methotrexate is the primary first-line therapy for RA due to its broad anti-inflammatory and immunomodulatory effects.[60] It suppresses immune-cell proliferation, shifts cytokine profiles toward anti-inflammatory activity, promotes adenosine release, disrupts pathogenic cell interactions, modulates NF-κB and JAK-STAT pathways, and reduces tissue-damaging enzymes. Methotrexate is highly effective and has a well-defined safety profile but lacks specificity. Newer immunomodulatory agents such as TNF-α inhibitors, IL-6 blockers and anti-angiogenic agents are more effective and have a wider margin of safety than methotrexate.[61] In addition, specific mechanisms to target (e.g., iron and ROS) in hemophilic arthropathy may be advantageous. These possibilities are explored below.

Iron/reactive oxygen species modulation

Data linking iron to c-myc/MDM2, chondrocyte apoptosis, and endothelial ferroptosis suggest exploring iron chelation, anti-oxidants, or ferroptosis regulators in joint-directed formats.

Cytokine-processing blockade

The iRhom2/ADAM17/TNF-α axis offers a genetically validated target to protect bone and synovium after bleeding; translation will require safety studies in the context of hemostasis.

Mast-cell modulation

Discovery of activated mast cells in hemophilic arthropathy synovium suggests that mast-cell stabilizers or tryptase inhibitors could be tested to reduce permeability and inflammatory amplification.

Stromal state reprogramming

Lessons from RA and OA indicate that fibroblast states are malleable; strategies that tilt hemophilic synovium away from catabolic/invasive programs (e.g., POSTN-like) and toward reparative programs (CILP-like) may aid cartilage preservation.

Cartilage survival signaling

The TNXB–AKT axis represents a cartilage-intrinsic pathway; AKT agonists or epigenetic interventions to preserve TNXB expression merit investigation as chondroprotective adjuncts after bleeds.

The "two-hit" frame and disease course

A helpful conceptualization is the "two-hit" hypothesis: (i) chemical injury caused by iron/heme and ROS causing chondrocyte apoptosis and synovial proliferation, is followed by (ii) inflammatory amplification in which the synovial membrane becomes a reservoir of inflammato-

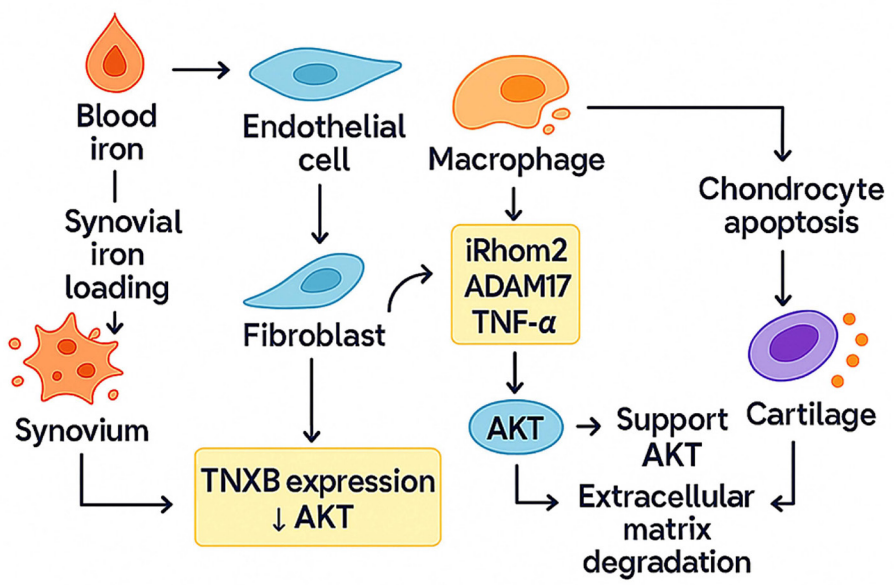

Figure 4. Integrated mechanisms of blood-induced joint disease leading to cartilage degeneration. Schematic overview of how intra-articular blood and iron drive progressive joint damage in hemophilic arthropathy. Iron accumulation within the synovium induces endothelial dysfunction and activates macrophages and fibroblasts, promoting inflammatory signaling mediated in part by iRhom2-dependent ADAM17 activity and tumor necrosis factor-α release. Concurrent suppression of TNXB results in impaired AKT signaling, reducing chondrocyte survival and extracellular matrix maintenance. The combined effects of inflammation, AKT pathway disruption, chondrocyte apoptosis, and matrix degradation culminate in irreversible cartilage damage characteristic of chronic hemophilic joint disease. ADAM17: a disintegrin and metalloproteinase domain-containing protein 17; AKT: protein iinase B; iRhom2: inactive rhomboid 2; TNF-α: tumor necrosis factor alpha; TNXB: tenascin XB.

ry mediators, transforming acute chemical damage into chronic inflammatory disease which then leads to structural damage to the osteochondrum.[62] The single-cell discoveries in hemophilic arthropathy operationalize this such that iron-driven endothelial ferroptosis (chemical hit) engages mast cells, fibroblast reprogramming, and macrophage TNF-α (inflammatory hit), culminating in self-sustaining pathology across synovium, cartilage, and bone.

Collectively, the data presented in this review substantiate the proposed pathways with histological, biochemical, and genomic convergence.

Clinical translation and future directions

Preventive administration of hemostatic agents (repeatedly or as a one-time treatment) to restore thrombin generation and normalize hemostasis thereby preventing bleeding remains the cornerstone of modern hemophilia management. Despite optimal prophylaxis, evidence indicates that clinically recognized as well as subclinical joint bleeding persists in a subset of people with hemophilia even with modern-day agents and regimens, pointing to the need for joint-specific, pathway-directed adjuncts to prevent arthropathy. Furthermore, global access to factor products, non-factor therapies and gene and cell therapies are limited to high-income countries and more than 80% of the world's hemophilia population do not have access to diagnosis and treatment. Based on the data above, testable hypotheses include the following.

Ferroptosis modulation in endothelium to protect microvasculature and reduce the propensity to rebleeding

Mitigating the detrimental effect of iron in the joint has been explored with the use of steroids[63] and iron chelators.[64] Glucocorticoids protect tissues from iron-induced injury primarily by suppressing inflammation, reducing ROS generation, stabilizing vascular barriers, and limiting synovial and stromal responses to iron, rather than by acting directly on iron-handling pathways.[65] A 1970 publication by Kisker and Burke[63] showed that a 5-day course of oral corticosteroids improved outcomes after acute hemarthrosis in boys receiving standard replacement therapy for that era. Intra-articular steroids have been used to relieve pain and reduce inflammation.[66] The ability of chelators such as deferasirox to enter the joint appears limited.[48] HMOX1 protects cells against oxidative stress including that induced by iron. Agents that induce HMOX1 by upregulating nuclear factor erythroid 2-related factor 2[67] such as sulforaphane, bardoxolone methyl, and dimethyl fumarate,[68] may be beneficial and warrant exploration. Alternatively, preventing iron-induced lipid peroxidation with activators of the glutathione peroxidase 4 pathway could be explored. Selenium supplementation, administration of N acetylcysteine, coenzyme Q10 or glutathione have not been studied. Activators of the AKT pathway[69] may also be beneficial but have not been evaluated in hemophilic arthropathy. These agents could be studied in a prophylactic setting or intra-articularly after bleeds. Finally, promotion of lymphangiogenesis favoring the physical removal of iron-filled macrophages may also have beneficial effects on cartilage. Chondrocyte regeneration has been demonstrated in animal models and may be possible in humans. The sex-determining region on the Y chromosome (SRY)-type high mobility group box-9 (SOX9) can promote chondrocyte regeneration and survival by influencing multicellular differentiation and anti-apoptotic signaling.[70]

Mast-cell stabilization

Mast-cell stabilization with drugs such as cromolyn (or its analogues) or with tryptase inhibitors[71] could reduce microvascular leakage and early inflammatory amplification. Although not studied in either animal models of hemophilia or people with hemophilia, hemophilia synovial single-cell sequencing[34] performed by Lin *et al*. identified activated perivascular mast cells as contributors to vascular permea-

bility, inflammatory amplification and bleeding susceptibility providing a mechanistic basis for why mast-cell stabilizers might be evaluated further in hemophilic arthropathy.

ADAM17/iRhom2/TNF-α axis blockade

Blockade of the ADAM17/iRhom2/TNF-α axis following joint bleeding may limit synovitis and preserve cartilage and bone. TNF inhibitors have been used to treat inflammatory conditions such as RA, psoriatic arthritis, juvenile idiopathic arthritis, inflammatory bowel disease, ankylosing spondylitis and psoriasis as well as other inflammatory conditions. Zhang *et al*. studied TNF inhibition in a mouse model and in people with hemophilia and chronic arthropathy and showed decreased synovial thickness and vascularity suggesting that anti-TNF may provide adjuvant protection in hemophilic arthropathy.[40] The TNF inhibitors approved by the United States Food and Drug Administration include infliximab, adalimumab, etanercept, golimumab, and certolizumab. These drugs should be studied both in a prophylaxis setting (prior to the onset of bleeding) and for treatment after bleeding has occurred. People with hemophilia have increased levels of circulating inflammatory markers compared to age- and weight-matched controls, with elevated levels of IL-6, C-reactive protein, and lipopolysaccharide-binding protein[72] providing a rationale for the use of these drugs in a preventative setting in the absence of bleeding.

Stromal state reprogramming

Leveraging insights from RA/OA, stromal state reprogramming can be attempted to nudge fibroblasts toward reparative phenotypes (CILP-like) and away from injurious program (POSTN-like) phenotypes.

Cartilage survival therapies

Cartilage survival therapies targeting the TNXB–AKT axis (AKT agonists, epigenetic modulators that preserve TNXB expression) could be used as chondroprotective strategies after hemarthrosis.

Conclusion

Research over two decades has transformed BIJD in hemophilia from a descriptive entity to a multi-cellular, multi-organ process initiated by blood and orchestrated by iron-centered molecular injury. The cascade unfolds across synovial fibroblasts as a result of iron inducing c-myc and MDM2 gene expression, macrophages triggering the iRhom2-ADAM17-TNF-α axis, mast cells activating perivascular endothelial cells and increasing permeability thereby increasing the likelihood or re-bleeding, endothelial cells injured by iron and signaling through the FTL-SCARA5 pathway, chondrocytes responding to ROS and undergoing apoptosis in response to TNXB–AKT activation, and bone osteopenia as a result of TNF-α-mediated effects. This integrated view provides a map of actionable nodes – iron/ROS handling, ferroptosis, mast-cell mediators, ADAM17/TNF-α processing, fibroblast state reprogramming, and TNXB–AKT cartilage survival – which can be layered on top of thrombin-generating therapies to prevent or attenuate joint damage in people with hemophilia. As precision biologicals and delivery systems advance, joint-targeted, mechanism-based interventions hold potential to convert hemarthrosis from a chronic driver of degeneration into a manageable, non-progressive event, improving long-term function and quality of life for people with hemophilia.

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Contributions

LAV conceptualized and wrote the first draft of this manuscript, conceptualized and designed the figures, and provided overall supervision. LAV and YD contributed equally to the methodology, investigation, revision and editing and both approved the final version.

Artificial intelligence

The figures were conceptualized and designed by one of the authors (LAV) *and created with the assistance of artificial intelligence using Microsoft 365 Co-Pilot: Microsoft. (2026). Copilot (GPT-4) [Large Language Model]. https://copilot.microsoft.com/*

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