

IN BRIEF

Arthropathy in People with Mild Hemophilia

E. Carlos Rodriguez-Merchan, MD, PhD

Research performed at Department of Orthopedic Surgery, La Paz University Hospital, Madrid, Spain

Received: 28 August 2025

Accepted: 23 December 2025

Abstract

In people with mild hemophilia (PwMH) it is essential to characterize the presence of articular complications to develop approaches to minimize the burden of the disease. To this end, on 5 August 2025 a literature search was conducted in PubMed using the keywords “arthropathy mild hemophilia.” Higher burden of arthropathy among PwMH compared to the general population has been reported. Arthropathy of the ankle in PwMH is frequent, is often disabling, and is due to episodes of bleeding into the ankle joint during childhood. It has been reported that 36.5% of PwMH have arthropathy. Patient age and factor levels are the most important risk factors associated with the development of arthropathy in PwMH. The risk of developing arthropathy increased by 7.9% for each additional year of the minimum factor VIII levels required to prevent total and spontaneous joint bleeds (19.2 IU/dL and 17.7 IU/dL, respectively) age and decreased by 7.7% for each 1 IU/dL increase in clotting factor. The minimum FVIII levels required to prevent total and spontaneous joint bleeds in PwMH have been identified (19.2 IU/dL and 17.7 IU/dL, respectively). The need for more careful monitoring of PwMH is required.

Level of evidence: III

Keywords: Arthropathy; Mild hemophilia; Prevalence; Prevention; Risk factors

Introduction

Mild hemophilia is characterized by factor levels between 0.05 and 0.40 IU/mL and is depicted by traumatic bleeds. Main matters associated with mild hemophilia are that it might not display for many years after birth, and that recognition might be low.¹

There are various ways to manage the hemophilic joints (shoulders, elbows hips, knee, ankles) in the initial stages of degeneration of the articular cartilage in the event that hematologic prophylaxis is useless in achieving no hemarthroses. Some of these are non-surgical, with which treatment must begin. These are Physical and Rehabilitation Medicine protocols. When these do not work, more aggressive treatment can be employed (radiosynovectomy, intra-articular injections of hyaluronic acid, arthroscopic debridement). Nonetheless, in the late stages of degeneration of the articular cartilage (advanced arthropathy), total joint arthroplasty of the great joints can

be required.²⁻⁵

Hemarthroses are a frequent and unusual adverse event associated with hemophilia, augmenting the risk of hemophilic arthropathy. Regarding mild hemophilia, it is essential to define and characterize the presence of articular complications to develop approaches to minimize the burden of the disease.⁶ People with mild hemophilia (PwMH) suffer sporadic bleeds and are less likely to be diagnosed early, and to receive adequate treatment.²

This article has attempted to define the joint complications suffered by PwMH with the aim of improving their prevention and treatment. To this end, on August 5, 2025, a literature search was conducted in PubMed using the keywords “arthropathy mild hemophilia.” A total of 208 articles were found, of which 15 were analyzed because they were directly related to the title of this article (inclusion criterion). The remaining 193 were excluded

Corresponding Author: Carlos Rodriguez-Merchan, Department of Orthopedic Surgery, La Paz University Hospital, Paseo de la Castellana 261, 28046-Madrid, Spain

Email: ecrmerchan@hotmail.com



THE ONLINE VERSION OF THIS ARTICLE
ABJS.MUMS.AC.IR



because they did not meet the aforementioned inclusion criterion.

Main body

Higher prevalence of arthropathy among PwMH compared to the general population has been reported. Therefore, the need for more careful monitoring of PwMH is required. Arthropathy of the ankle in PwMH is frequent, is often severe and disabling, and is due to episodes of bleeding into the ankle joint during childhood. It has been reported that 36.5% of PwMH have arthropathy. Patient age and factor

levels appeared to be the most important risk factors associated with the development of arthropathy in PwMH. The minimum FVIII levels required to prevent total and spontaneous joint bleeds in PwMH have been identified (19.2 IU/dL and 17.7 IU/dL, respectively). Detailed information on existing publications in PubMed on arthropathy in individuals with mild hemophilia is shown in [Table 1].⁷⁻²⁰

Table 1. Publications on arthropathy in people with mild hemophilia (PwMH)

AUTHORS [REFERENCE]	YEAR	METHODS	RESULTS	CONCLUSIONS
Gilchrist et al [9]	1977	Severe degenerative joint disease developed in three adults with mild to moderately severe hemophilia A.	Bilateral THA was required in one patient, unilateral THA in the second, and a recommendation for bilateral TKA in the third.	These authors suggested the need for more careful monitoring of individuals who have mild hemophilia.
Streit et al [10]	1984	These authors investigated the response to intranasal administration of 260 micrograms of DDAVP in 28 individuals with either mild hemophilia A or von Willebrand's disease. Six individuals with mild hemophilia A responded, and 6 did not.	In the group with von Willebrand's disease 6 responded well, 4 responded partially and 6 did not respond. Knowledge of the severity of the disease did not allow these authors to predict the response, and therefore every subject should be tested individually.	Intranasal DDAVP was utilized with success for bleeding into the knee joint, muscle hematoma and hematuria.
Bovill et al [11]	1985	These authors presented the rare occurrence of an inhibitor of FVIII procoagulant arising in an individual with mild hemophilia A and rheumatoid arthritis. The inhibitor was transient and behaved like a low titer, type II FVIII procoagulant inhibitor.	In vitro studies confirmed the type II-like interaction of this inhibitor with the FVIII procoagulant molecule. FVIII procoagulant antigen level was equal to the FVIII procoagulant activity, which excluded dysproteinemia as the cause.	This patient's HLA type has no known association with abnormal immune responsiveness or autoimmune disease.
Bairey et al [12]	1991	These authors described three individuals with mild FIX, X or XI deficiency who presented with spontaneous hemarthrosis. All underwent joint puncture with subsequent worsening of the hemarthrosis in the affected joint.	This report indicated that: even mild coagulation factor deficiency might be associated with hemarthrosis; individuals with suspected hemarthrosis should undergo routine screening coagulation tests prior to joint puncture; and any abnormalities in the screening tests indicate a need for further assessment of the coagulation status.	In individuals with mild hemophilia puncture of the joint should be deferred and specific therapy started immediately.
Aydogdu et al [13]	2001	A 15-year-old boy with mild hemophilia who regularly participated in contact sports presented with right hip pain radiating to the groin and buttock areas and difficulty in walking.	Conventional radiography disclosed a heterotopic new bone formation in the adductor region. The reformatted and three-dimensional reconstructed images of CT scans detailed an incomplete pelvi-femoral bone bridge formation in the quadratus femoris muscle, which was located very close to the sciatic nerve but did not cause any clinical symptoms.	Postural exercises and clinical survey were selected as the primary treatment.
Bauduer et al [14]	2001	A mild hemophilia A (FVIII 10%) was discovered in a 73-year-old man during the preoperative hemostasis tests before a TKA for treatment of degenerative senile arthropathy. No history of previous abnormal bleeding was noted despite several previous challenging surgical procedures. Acquired hemophilia was ruled out and no other cases of hemophilia were found in the family.	The surgery was successfully carried out under recombinant FVIII aimed at accomplishing an FVIII level above 60%. This therapy induced the transient appearance of low-titer FVIII antibodies. A still unpublished mutation within the exon 3 (Gly73Ala) was encountered with molecular studies.	This case report underlined the importance of hemostasis tests before high-risk bleeding surgical procedures even in elderly individuals without a past history of hemorrhagic tendency.

Table 1. Continued

Ling et al [15]	2011	These authors studied ankle arthropathy in 34 individuals with mild/moderate hemophilia A. The individuals were evaluated for the presence and severity of pain, and by the physical and radiological scoring systems for the assessment of hemophilic arthropathy recommended by the WFH.	Of the 34 individuals, 16 (47%) had ankle pain which was of moderate to severe degree in nine individuals, and associated with limitation of physical activities in 13 individuals. Of 33 individuals examined by radiology, 17 (52%) were positive for ankle arthropathy, and of these, 16 were also positive by the physical score. The presence and severity of ankle arthropathy was more common in individuals with a one-stage FVIII level of less than or equal to 11 IU/dl. There was a significant relationship between the presence of ankle arthropathy and a history of bleeds into the ankle joint as a child.	These authors concluded that arthropathy of the ankle in hemophilic patients with mild hemophilia was common, was often severe and disabling, and was due to episodes of bleeding into the ankle joint during childhood.
Osooli et al [8]	2017	This was a register-based cohort study. The aim of this study was to compare the incidence, age at diagnosis and surgery for arthropathy and related hospitalizations between people with mild hemophilia and the general population in Sweden. Eligible participants were those with mild hemophilia born between 1941 and 2008 and a randomly selected, birthdate and sex-matched comparison group from the general population. Follow-up was from birth (or earliest 1984) until death, emigration or end of the study in 2008. Data on arthropathy were obtained from a national patient register.	Overall, 315 people with hemophilia and 1529 people in the comparison group were included. Participants with hemophilia born between 1984 and 2008 had a ninefold and 16-fold increased incidence of arthropathy-related hospital admission and arthropathy diagnosis respectively. None in this cohort experienced surgery. Among participants with hemophilia born prior to 1984, the rates of arthropathy diagnosis and surgery of the index joints (knee, elbow, ankle) were increased twofold and fivefold respectively.	The data of this study suggested a higher burden of arthropathy among individuals with mild hemophilia compared to the general population.
De la Corte-Rodriguez et al [16]	2022	This was an observational, cross-sectional cohort study of 85 people with mild hemophilia. Its purpose was to examine the risk factors associated with arthropathy and to predict their presence and degree of involvement in people with mild hemophilia. Patient variables (age, body mass index, hemophilia type, genetic mutations, baseline factor levels, age at diagnosis, history of inhibitor, level of physical activity and years of practice, history of hemarthrosis and muscle hematoma) were analyzed and related to the presence or absence of arthropathy and the degree of arthropathy (measured with HJHS and HEAD-US).	Some 36.5% of people with mild hemophilia had arthropathy. The variables that showed an independent association with the presence of arthropathy were patient age (median 42 years) and clotting factor levels (median 10.5 IU/dL). The risk of developing arthropathy increased by 7.9% for each additional year of age and decreased by 7.7% for each 1 IU/dL increase in clotting factor. When arthropathy developed, its degree of involvement might have been influenced by the type of physical activity performed.	Patient age and factor levels appeared to be the most determinant risk factors associated with the development of arthropathy in mild hemophilia. In patients with arthropathy, physical activities with a low risk of bleeding were the most recommended.
Zwagemaker et al [17]	2022	This cross-sectional study included individuals with non-severe hemophilia A aged 24-55 years. Its purpose was to investigate their joint status. It was assessed by MRI of the elbows, knees, and ankles and IPSC scores. Lifetime joint bleeding history was collected from medical files.	In total, 51 individuals were included, of whom 19 (37%) had moderate and 32 (63%) had mild hemophilia. Patients had a median age of 43 years, a median FVIII activity of 10 IU/dl and a median AJBR of 0.0. Soft-tissue changes (IPSC subscore > 0) in the elbows, knees, and ankles were present in 19%, 71%, and 71% of patients, respectively. Osteochondral changes (IPSC subscore > 0) in the elbows, knees, and ankles were present in 0%, 20%, and 35% of patients, respectively. In 14% of bleed-free joints, hemosiderin depositions were observed. Age and AJBRs were most strongly associated with the IPSC score.	This study demonstrated that a substantial proportion of adults with non-severe hemophilia had joint changes on MRI despite low joint bleeding rates.

Table 1. Continued

Kloosterman et al [18]	2022	These authors aimed to assess the bleeding phenotype of persons with non-severe hemophilia and to analyze the association between baseline FVIII/IX levels and the joint bleeding rate. In the DYNAMO (Dynamic Interplay Between Bleeding Phenotype and Baseline Factor Level in Moderate and Mild Hemophilia A and B) study, an international multicenter cohort, these authors included males with non-severe hemophilia (FVIII/IX, 0.02-0.35 IU/mL) aged 12 to 55 years. Information on age at first treated (joint) bleed, ABRs, and AJBRs were collected from the medical files. The association between baseline FVIII/IX levels and the joint bleeding rate was assessed by using a frailty model for recurrent events.	In total, 304 individuals (70 with moderate hemophilia and 234 with mild hemophilia) were included. The median age was 38 years, and the median baseline FVIII/IX level was 0.12 IU/mL. In total, 245 (81%) individuals had experienced at least 1 bleed, and 156 (51%) had experienced at least 1 joint bleed. The median age at first bleed and first joint bleed was 8 and 10 years, respectively. The median ABR and AJBR were 0.2 and 0.0. From baseline FVIII/IX levels 0.02 to 0.05 IU/mL to >0.25 IU/mL, the median ABR decreased from 0.6 to 0.1 and the AJBR from 0.2 to 0.0. Baseline FVIII/IX was inversely associated with the joint bleeding rate.	Low bleeding rates were observed in individuals with non-severe hemophilia. However, one-half of all adolescents and adults had experienced a joint bleed.
Daffunchio et al [7]	2023	Observational, cross-sectional cohort study. The aim of this study was to evaluate the incidence, risk factors and QoL associated with arthropathy in people with mild hemophilia. Data were collected in a single interview and evaluated by a physiotherapist and an orthopedist and analyzed on demographics; baseline factor levels; as well as clinical (HJHS, HEAD-US, radiological Pettersson score, pain (VAS) and QoL evaluations. These authors defined arthropathy when at least one of the joints shown with a HEAD-US score ≥ 1 .	Eighty-five patients and 510 joints were included. Patients' mean age was 35.9 years. Median age was 44.2 in patients with arthropathy versus 14.9 in patients without; the difference was statistically significant. In patients over 20 years old, 90.5% showed arthropathy. Only 24 (28%) patients had no joint damage (HEAD-US = 0), and 61 (72%) had at least one joint with a HEAD-US ≥ 1 . The ankle was the most affected joint. Patient age was found to be the most important risk factor associated with the development of arthropathy.	Joint damage as a result of prior hemarthrosis was the most relevant factor associated with lower QoL and emphasized the importance of early diagnosis and appropriate management in this particular population.
Agosti et al [19]	2023	This study aimed to identify the minimum FVIII level necessary to prevent joint bleeds in patients with hemophilia A. In this retrospective study, patients with congenital mild hemophilia A treated on demand, aged ≥ 16 years, with no history of FVIII inhibitors, were enrolled.	These authors investigated 270 male patients with a median age of 45 years (16-88) and median lifelong FVIII of 21 IU/dL. One hundred patients (37%) had a lifelong history of at least 1 joint bleed. The mean AJBR and spontaneous AJBR were 0.016 and 0.001, respectively. After adjusting for age, for each IU/dL increase in FVIII, there was a 6% reduction in AJBR and an 11% reduction in spontaneous AJBR. The minimum FVIII levels needed to prevent lifelong any joint bleeds and spontaneous joint bleeds resulted to be 19.2 IU/dL and 17.7 IU/dL, respectively.	In this large cohort of people with mild hemophilia A, these authors identified the minimum FVIII levels needed to prevent total and spontaneous joint bleeds (19.2 IU/dL and 17.7 IU/dL, respectively).
Chiari et al [6]	2024	A retrospective chart review was conducted for patients with mild hemophilia. Its aims were to characterize the prevalence, clinical characteristics of joint bleeds, and risk factors that may lead to hemarthrosis in people with mild hemophilia.	The medical records of 70 patients were reviewed. Eighty one percent were male and 19 percent were female. Twenty individuals with mild hemophilia had a history of joint bleeding, 13 were traumatic bleeds, 7 were spontaneous. The age of first joint bleed ranged from 4 to 58 years old, with an average age of 20.8-years old. Ten patients developed joint bleeds between the ages of 10 and 20 years old. The most common locations of joint bleeding were the knee (N=11) and ankle (N=7). Eight of 70 patients had hepatitis C (HCV), and 6 experienced joint bleeding.	In this study, almost one third of patients with mild hemophilia experienced joint bleeding, often without history of trauma. Joint ROM was abnormal in more than a third of the patients with mild hemophilia regardless. These data highlight the need for ongoing evaluation and characterization of joint health in individuals with mild hemophilia. Twenty-nine percent of individuals with mild hemophilia had history of joint bleed. People with hemophilia and mild

Table 1. Continued

				diseases with previous or current hepatitis C had higher likelihood of joint bleeding. Approximately 15% of people with hemophilia and mild diseases had abnormal joint examinations without a confirmed history of joint bleeding.
Rodeghiero et al [20]	2025	Publications of unselected cases with bleeding history available from birth to the time of publication were considered to estimate the incidence of a first severe bleeding event.	More than 20% of cases with mild or moderate hemophilia met the criteria for severe bleeding disorder by experiencing joint or non-joint severe bleeding events. Furthermore, a significant proportion of patients developed an inhibitor against FVIII or IX.	These results substantiate the criticism of the current classification of hemophilia and argue for the adoption of a new classification that takes into account bleeding phenotype in addition to basal clotting activity.
THA=total hip arthroplasty; TKA=total knee arthroplasty; FVIII=factor VIII; DDAVP=desmopressin; HLA=human leukocyte antigen; CT= computerized tomography; WFH=World Federation of Hemophilia; HJHS=Hemophilia Joint Health Score; HEAD-US= Hemophilia Early Arthropathy Detection with Ultrasound; MRI=magnetic resonance imaging; IPSTG=International Prophylaxis Study Group; ABRs=annual bleeding rates; AJBR=annual joint bleeding rate; QoL=quality of life; VAS=visual analogue scale; HCV=hepatitis C virus; ROM= range of motion.				

Conclusion

About 37% of PwMH have arthropathy. More careful monitoring of PwMH is required. Arthropathy of the ankle in PwMH is frequent.

Acknowledgement: N/A

Authors Contribution: ECR-M has done all steps.

Declaration of Conflict of Interest: The author does NOT have any potential conflicts of interest for this manuscript.

Declaration of Funding: The author received NO financial support for the preparation, research, authorship, and publication of this manuscript.

Declaration of Ethical Approval for Study: Our institution

does not require ethical approval for reporting retrospective studies.

Declaration of Informed Consent: The author declares that there is no information (names, initials, hospital identification numbers, or photographs) in the submitted manuscript that can be used to identify patients.

E. Carlos Rodriguez-Merchan MD ¹

1 Department of Orthopedic Surgery, La Paz University Hospital, Paseo de la Castellana 261, 28046-Madrid, Spain

References

- Benson G, Auerswald G, Dolan G, et al. Blood Transfus. 2018;16(6):535-544. doi: 10.2450/2017.0150-17.
- De la Corte-Rodriguez H, Rodriguez-Merchan EC. The role of physical medicine and rehabilitation in haemophiliac patients. Blood Coagul Fibrinolysis. 2013;24(1):1-9. doi: 10.1097/MBC.0b013e32835a72f3.
- Carulli C, Rizzo AR, Innocenti M. Hip Arthropathy in haemophilia. J Clin Med. 2017;6(4):44. doi: 10.3390/jcm6040044.
- Mortazavi SJ, Bagheri N, Farhoud A, Hadi Kalantar S, Ghadimi E. Total knee arthroplasty in patients with hemophilia: what do we know? Arch Bone Jt Surg. 2020;8(4):470-478. doi: 10.22038/abjs.2019.42247.2149.
- Rodriguez-Merchan EC. The current role of ankle arthrodesis in hemophilic patients. Arch Bone Jt Surg. 2022;10(2):129-134. doi: 10.22038/abjs.2020.47865.2366.
- Chiari JB, Prozora S, Feinn R, Louizos E, Gallagher PG, Bona R. Joint bleeds in mild hemophilia: prevalence and clinical characteristics. Haemophilia. 2024;30(2):331-335. doi: 10.1111/hae.14939.
- Daffunchio C, Landro ME, Galatro G, et al. How mild is mild haemophilia? Haemophilia. 2023;29(2):530-537. doi: 10.1111/hae.14750.
- Osooli M, Lövdahl S, Steen Carlsson K, et al. Comparative burden of arthropathy in mild haemophilia: a register-based study in Sweden. Haemophilia. 2017;23(2):e79-e86. doi: 10.1111/hae.13166.
- Gilchrist GS, Hagedorn AB, Stauffer RN. Severe degenerative joint disease. Mild and moderately

- severe hemophilia A. *JAMA*. 1977;238(22):2383-2385. PMID: 578865.
10. Streit A, Furlan M, Beck EA. [Desamino-8-D-arginine vasopressin nose drops in the treatment of mild hemophilia A and von Willebrand's disease]. *Schweiz Med Wochenschr*. 1984;114(40):1389-1391. PMID: 6333722.
 11. Bovill EG, Burns SL, Golden EA. Factor VIII antibody in a patient with mild haemophilia. *Br J Haematol*. 1985;61(2):323-328. doi: 10.1111/j.1365-2141.1985.tb02832.x.
 12. Bairey O, Shaklai M, Inbal A. Haemarthrosis in patients with mild coagulation factor deficiency. *Blood Coagul Fibrinolysis*. 1991;2(5):669-671. doi: 10.1097/00001721-199110000-00014.
 13. Aydogdu S, Memis A, Kavakli K, Balkan C. The pelvi-femoral incomplete bone bridge in a patient with mild haemophilia. *Haemophilia*. 2001;7(2):224-226. doi: 10.1046/j.1365-2516.2001.00496.x.
 14. Bauduer F, Ducout L, Bendriss P, Falaises B, Lavergne JM. Mild haemophilia A discovered in a previously multi-operated 73-year-old man: characterization of a new mutation. *Haemophilia*. 2001;7(4):419-421. doi: 10.1111/j.1365-2516.2001.00512.x.
 15. Ling M, Heysen JP, Duncan EM, Rodgers SE, Lloyd JV. High incidence of ankle arthropathy in mild and moderate haemophilia A. *Thromb Haemost*. 2011;105(2):261-268. doi: 10.1160/TH10-07-0492.
 16. De la Corte-Rodriguez H, Rodriguez-Merchan EC, Alvarez-Roman MT, Martin-Salces M, Rivas-Pollmar I, Jimenez-Yuste V. Arthropathy in people with mild haemophilia: exploring risk factors. *Thromb Res*. 2022;211:19-26. doi: 10.1016/j.thromres.2022.01.010.
 17. Zwagemaker AF, Kloosterman FR, Hemke R, et al. Joint status of patients with nonsevere hemophilia A. *J Thromb Haemost*. 2022;20(5):1126-1137. doi: 10.1111/jth.15676.
 18. Kloosterman FR, Zwagemaker AF, Bagot CN, et al. The bleeding phenotype in people with nonsevere hemophilia. *Blood Adv*. 2022;6(14):4256-4265. doi: 10.1182/bloodadvances.2022007620.
 19. Agosti P, Siboni SM, Scardo S, Torri A, Gualtierotti R, Peyvandi F. Minimum factor VIII levels to prevent joint bleeding in mild hemophilia A. *Blood Adv*. 2023;7(23):7209-7215. doi: 10.1182/bloodadvances.2023011366.
 20. Rodeghiero F, Ghiotto L, Pontalto L, et al. Mild or moderate hemophilia is not always a mild or moderate bleeding disorder: Back to the clinical phenotype. *Hemasphere*. 2025;9(3):e70111. doi: 10.1002/hem3.70111.