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IN BRIEF

Bone Fractures in People with Hemophilia

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Received: 4 February 2025 *Accepted: 14 April 2025*

Abstract

The existing literature on bone fractures in people with hemophilia (PWH) states that they should be treated in the same way as in healthy individuals but with perioperative hemostasis control through intravenous infusion of the deficient coagulation factor (factor VIII in hemophilia A, factor IX in hemophilia B) at appropriate doses and for the necessary duration. It has also been found that fractures in PWH are more frequent than in normal individuals, probably due to suffering from osteoporosis. The healing time for fractures in PWH is similar to that of the general population. It should be noted that some fractures in PWH are pathological due to the presence of hemophilic pseudotumors that cause erosion of the affected bone. These fractures should also be treated as pathological fractures of any other etiology. Finally, the risk of acute compartment syndrome associated with bone fractures in PWH should never be forgotten.

Level of evidence: III

Keywords: Bone fracture, Complications, Hemophilia, Treatment

Introduction

People with hemophilia (PWH) can suffer bone fractures. Due to the congenital deficit of some coagulation factor, mainly factor VIII (hemophilia A) and factor IX (hemophilia B), PWH have a high risk of bleeding when they need surgical treatment of bone fractures if adequate hemostasis is not achieved by intravenous injection of the deficient clotting factor.[1,2]

The purpose of this paper is to review the prevention and management of bone fractures in PWH. For this purpose, on January 29, 2025, a literature search was carried out in PubMed using "hemophilia fractures" as keywords. Two hundred and fifty-three articles were found, of which only 24 were finally analyzed because they were strictly related to the title of this article. Therefore, this is a narrative review of the literature. The most important data from the articles published on fractures in PWH are shown in [Table 1].[3-26]

Table 1. Fractures in people with hemophilia (PWH) in the literature.[3-26]

AUTHORS [REFERENCE]	YEAR	METHODS	RESULTS	CONCLUSIONS
Boni and Ceciliani [3]	1976	Eight cases of fractures in PWH were analyzed.	The clinical and radiological features, behavior and response to treatment indicated that they were normal, not pathological fractures.	If fractures in PWH are treated early and correctly both from a hematological and orthopedic point of view, the results are comparable with those in normal subjects.

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

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Table 1. Continued

Tozzi et al [4]	1978	Case report	A case of femoral fracture in diseased bone in an adult hemophilic patient with relatively advanced arthropathy was reported.	These authors described the principles underlying the relevant orthopedic surgery, combined with suitable hematological preparation.
Boardman and English [5]	1980	Twenty-two PWH A were successfully treated for fractures and dislocations without complication in the last 10 years, with the aid of recently developed methods of maintaining hemostasis, and conventional methods of reduction and immobilization.	Most injuries were managed "conservatively," but 4 patients had operations. All the injuries healed in average time. A factor VIII level of 30% was maintained for the first 2 to 4 days for stable fractures and for 5 to 7 days for unstable fractures, but patients requiring operations were covered to a level of 60% for 2 weeks. Factor VIII concentrates were not given to 2 patients with inhibitors.	Excessive bleeding occurred in one of the patients with inhibitors and in another in whom replacement therapy was delayed, but bleeding was not a problem in the remaining patients.
Wolf and Lovrien [6]	1982	Nine PWH A suffered 16 fractures. Four patients had severe hemophilia (factor VIII less than 1%) and five had moderate or mild hemophilia (factor VIII between 4% and 25%).	Two patients developed skeletal pseudotumors after their fractures. One patient developed neurapraxia. Fractures in hemophiliacs should be treated promptly with 25 units/kg/day of factor. Fractures of the upper limb should be maintained at this dose for seven days; lower extremity fractures should be treated with factor for 14 days. Orthopedic management should be the same as used for nonhemophiliacs.	Skeletal pseudotumors should be managed with prolonged factor administration and immobilization until radiographic evidence of healing occurs.
Markakis et al [7]	1984	The authors give a review of the most frequent forms of hemophilia and describe the problems connected with fractures in patients suffering from hemophilia, the treatment methods and the indications for conservative or surgical therapy.	The evaluation of 25 cases with hemophilia treated between 1972 and 1982 for one or more fractures showed that the primary disease does not essentially influence the healing process with the understanding that an early and sufficient substitution of the missing coagulation factors is administered.	By means of a correct pretreatment (infusions of plasma or coagulation factors), these authors obtained good results in most of their cases.
Ishiguro et al [8]	1998	These authors presented three surgical cases of pseudotumors involved in a pathological fracture in the extremities.	All cases showed a favorable postoperative course. It was stated that if the preoperative management is appropriately designed, a limb salvage operation for a pathological fracture due to a pseudotumor could be carried out successfully.	Before choosing amputation of a limb, the orthopedic surgeon should consider the possibility of limb salvage.
Pruthi et al [9]	2000	hese authors described a patient with mild hemophilia B who developed symptomatic venous thromboembolism after hip arthroplasty for a traumatic fracture.	A deep vein thrombosis developed in the operated leg while he was receiving a high-purity factor IX concentrate. Subsequently, he was determined to be a heterozygous carrier for the factor V Arg506Gln (Leiden) mutation. This case illustrated the importance of providing thromboprophylaxis for all patients with hemophilia receiving coagulation factor replacement and who undergo surgical procedures known to be associated with a high risk of venous thromboembolism.	In patients with hemophilia and a family history of venous thromboembolism, preoperative screening for the presence of the factor V Arg506Gln mutation and other thrombophilias may be useful.
Rodriguez-Merchan [10]	2002	In this review article it was stated that the goal of fracture treatment is to obtain an optimal outcome, with the patient's return to full activity as soon as possible.	Internal stabilization was indicated in most displaced fractures in adults, whereas external fixation remained the best choice for initial stabilization with severe soft-tissue injuries.	If a fracture is correctly treated in a hemophilic patient, it will progress to consolidation in a similar time-frame to fractures occurring in the general population.
Lee et al [11]	2007	These authors described the management of eleven patients with fracture neck of femur. Excepting one patient all had severe hemophilia A. Nine patients were less than 50 years of age. Eight out of eleven patients had fracture after trivial trauma.	Nine patients had closed reduction and one patient open reduction. The patient with non union had a valgus osteotomy. All fractures united. The average time to union was 11 weeks. These authors followed either a low dose intermittent or a low dose continuous infusion factor support protocol for the management of these patients. The median dose of factor support was 252 U/kg. The average duration of factor support was 9 days. Two patients had aggravation of preexisting knee stiffness following postoperative immobilization. No other major complication was observed in this cohort of patients.	Management of fracture neck of femur in PWH is no different from general population if an adequate hemostasis is achieved.

Table 1. Continued

Leblanc et al [12]	2012	These authors stated that interprosthetic fractures of the humerus were rare, and that revisions of total elbow arthroplasty components in these cases were difficult. These authors reported the first case of a patient with hemophilia who underwent a revision with a tibial allograft prosthetic composite without the need for hardware augmentation.	A 43-year-old Caucasian man with a history of hemophilia and transfusion-related human immunodeficiency virus and hepatitis B and C presented with an interprosthetic fracture of his humerus after months of pain between his total elbow and total shoulder arthroplasties. Because of the poor remaining bone stock available in his distal humerus, a revision using a barrel-staved tibial allograft prosthetic composite was performed. Factor VIII level was optimized before the operation and the patient suffered no major long-term complications at 28 months. His only complication was an incomplete radial nerve palsy that ultimately recovered and left him with some numbness on the dorsum of his hand.	Careful use of an allograft prosthetic composite was a very reasonable option. These authors successfully performed revision total elbow arthroplasty for a patient with hemophilia with an interprosthetic fracture using a tibial allograft and no additional fixation, which resulted in his return to full activities of daily living, minimal pain and full incorporation of the allograft to host bone.
Anagnostis et al [13]	2013	These authors stated that hemophilia A and B had been associated with increased prevalence of low BMD. However, no study had so far evaluated the effects of anti-osteoporotic therapy on BMD in hemophilia. The primary endpoint of this prospective study was to estimate the effect of 12-month therapy of oral ibandronate 150 mg/month on BMD in patients with hemophilia A and B. Secondary endpoint was its effect on bone turnover markers (BTM) of bone resorption [serum C-terminal telopeptide of type 1 collagen (sCTX), tartrate-resistant acid phosphatase band 5b] and bone formation (osteocalcin and bone-specific alkaline phosphatase).	Ten adult patients with T-score < -2.5 SD or Z-score < -2 and/or increased risk of fracture according to FRAX model were included. All received 1,000 mg/day calcium carbonate with 800 IU/d cholecalciferol. Males with hemophilia A (N = 7) or B (N = 3) (mean age 43.5 years) were studied. Ibandronate resulted in an increase in lumbar BMD (from 0.886 to 0.927 g/cm2, 4.7%, p = 0.004). No change in BMD of total hip (from 0.717 to 0.729 g/cm2, p = 0.963) or femoral neck (0.741 to 0.761 g/cm2, p = 0.952) was noticed. Ibandronate led to a decrease in sCTX (from 0.520 to 0.347 ng/ml, -29.9%, p = 0.042). No change was observed in other BTM. Ibandronate was generally well-tolerated.	Ibandronate significantly improved BMD in lumbar spine and reduced bone resorption in adults with hemophilia at increased risk of fracture. Its effect on hip BMD and bone formation markers was not significant.
Lin et al [14]	2015	These authors evaluated the efficacy of external fixators (EFs) for management of open fractures of tibia and fibula in patients with hemophilia A. This was a retrospective therapeutic study.	These authors described the use of EF (Orthofix uniplanar fixators) in five patients (mean age: 31.4 years) with hemophilia A suffering from open fracture of tibia and fibula (Gustilo classification ranging from II to IIIA). The average time to union was 23 weeks. Much lower levels were subsequently maintained till wound healing. The average total factor consumption was 358.30 IU kg(-1), administered over a period of 14.2 days. There were no major complications related to EF.	EFs can be used safely and effectively in management of open fractures of tibia and fibula in patients with hemophilia A.
Huang et al [15]	2015	These authors investigated the characteristics and perioperative management of hemophilia patients with fracture. Retrospectively, these authors analyzed 8 patients with hemophilia combined with fracture. Six patients were with hemophilia A and two with hemophilia B; based on the severity of hemophilia, 2 cases were light, 3 moderate and 3 severe; based on the location of fracture, 4 cases were femoral neck fractures, 1 femoral intertrochanteric fracture, 1 bilateral distal femur fractures, 1 tibiofibula fracture, and 1 humerus intercondylar fracture. Blood coagulation factor replacement therapy was conducted preoperatively, intraoperatively and postoperatively, All the patients underwent closed or open reduction and internal fixation or joint replacement. Also, these authors analyzed the perioperative complications and observed whether the fracture healed.	he average age was 33.5 years; In 6 cases, fractures occurred at femur, accounting for 75% of all the fractures; Femoral neck fracture was treated by closed reduction and hollow screws fixation; femoral intertrochanteric fracture, distal femur fracture, and tibiofibula fracture were treated by open reduction and internal fixation with plate; humerus intercondylar fracture was treated by elbow joint replacement. Intraoperative bleeding was 262 mL on average; perioperatively, the average use of factor VIII/APCC was 358 U/kg. Postoperatively, poor wound healing was observed in 2 patients, and the condition improved after symptomatic treatment; In patients with internal fixation, all the fractures united, and the average healing time was 14 weeks. No complications such as fixation loosening or rupture occurred after internal fixation.	Hemophilia combined with fracture mainly occurred in the young, and the site of fracture was given priority to femur. With perfect preoperative preparation, on the basis of the replacement therapy, hemophilia combined with fractures was safe for surgical treatment, and fracture healing was good. But the risk of poor wound healing was high.
Candiotto et al [16]	2015	These authors presented the case of a 52-year old Caucasian male, admitted with posttraumatic supracondylar fracture of the left femur (and severe hemophilia A (factor VIII:C<1%, *F9* mutation: int22inv) with high-titer inhibitors. It was decided to proceed to surgical reduction of the fracture.	These authors corrected the knee flexion contracture at the time of surgical fixation of the fracture. They used factor VIII concentrates to obtain haemostatic control at the beginning when the risk of bleeding is higher and the best possible hemostasis is necessary. Once replacement with factor VIII was no longer effective, as expected, a continuous infusion of rFVIIa (recombinant factor VII activated) was started.	Full extension of the leg permitted easier walking than flexion and that is why these authors chose to realign the femur by osteotomy to enable walking without crutches. This case demonstrated that the best results may be obtained by close cooperation between hematologists and orthopedic surgeons.

Table 1. Continued

Anagnostis et al [17]	2015	Despite the increasing evidence regarding its association with low BMD both in adults and children, hemophilia A or B had not yet been considered among the classic causes of secondary osteoporosis.	Although the exact mechanisms were not fully elucidated, physical inactivity and vitamin D deficiency seemed to play a fundamental role for such an association. Viral infections and arthropathy further compromise bone mass. Except for low BMD, PWH seemed to be at increased risk for fracture and falls.	The FRAX tool may be of value in this population, for the estimation of fracture risk. Regular exercise, prophylactic factor replacement therapy in severe hemophilia, fall prevention strategies and optimization of calcium and vitamin D intake were recommended. In any case, individualized multidisciplinary approach and careful assessment and management of fracture risk were recommended.
Caviglia et al [18]	2015	These authors presented their 28 years experience treating PWH who suffered fractures and evaluate the impact of access to treatment. In the period 1986-2013, 151 fractures in 141 PWH were treated, 125 patients type A (88.7%), 12 type B (8.5%) and 4 (2.8%) with von Willebrand's disease. For the sake of analysis these authors divided the fractures in five groups: 1986-1990: 25, 1991-1995: 35, 1996-2001: 33, 2002-2007: 31, and 2008-2013: 27; and classified the fractures in lower limb and upper limb. These authors also considered the age at which the fractures occurred.	However the incidence of presentation of the fractures of the upper limb and lower limb changed through the years, being more frequent in the lower limb in the first period analyzed (76% lower limb vs. 24% upper limb) and in the upper limb in the latter one (63% upper limb vs. 37% lower limb), the difference was statically significant (p = 0.0168). In the relation with the age, the 1986-1990 cohort vs. 2008-2013 cohort reached statistical significance (p = 0.035). Regarding treatment, 121 fractures were treated in a non invasive way, the others 30 fractures, were treated with internal fixation. The patient treated with internal fixation had less mal-alignment, and delay consolidation.	These authors showed a higher incidence of lower limb fractures in the first period analyzed (1986-1990), over time, the ratio lower limb/upper limb changed as upper limb fractures became more frequent. This change is due to the access of the treatment and specifically to the prophylaxis. Fractures in PWH have changed their pattern, becoming more common in the upper limb than in the lower limb, lowering the age at which they occur and being less frequent. These authors believed that the advent of new and accessibly treatments, decreased the development of orthopedic complications and favored the improvement in quality of life of PWH.
Gay et al [19]	2015	These authors performed a retrospective analysis of all male patients with hemophilia A and B that were seen at The Hemophilia Center at Oregon Health & Science University (OHSU) from 1 January 2003 to 31 December 201. The retrospective cohort included a total of 382 patients (316 with hemophilia A and 66 with hemophilia B). Data was gathered from a total of 2053 patient years of observation. Incidence rates (IR) and relative risk (RR) of bone fractures were calculated. The results were compared to those from a large prospective cohort study in the United States that measured gender- and age-specific fracture rates in the general population.	The fracture incidence in hemophilia subjects was considerably higher, at 24.8 fractures per 1000 patient-years, than in the control population, at 9.6 fractures per 1000 patient years. This correlated to a significantly greater relative risk of fracture in the hemophilia population compared with the control population. Additionally, subjects with mild to moderate hemophilia had a significantly decreased risk of fracture compared to those with severe disease. There was a trend toward higher fracture incidence in PWH with an inhibitor compared to those with no inhibitor, at 35.9 vs. 21.7 fractures per 1000 patient years, but no statistically significant difference in fracture risk was found. The incidence of bone fractures was similar between patients with hemophilia A and B with 22.9 and 23 fractures per 1000 patient-years respectively. Fracture risk was also not significantly different between the hemophilia A and B cohorts. In this cohort, fracture risk increased with age. People older than 31 years were more than twice as likely to suffer a fracture than those younger than 31 years of age. Age also had a dose effect, with risk of fracture increasing about 1.3% per year of age.	Despite a known propensity for decreased BMD in PWH, there is a paucity of data describing how this translates into fracture risk. This study demonstrated that fracture rates were elevated significantly in hemophilia subjects and represents an important co-morbidity to be considered when caring for this population. More studies were needed to address how clinical bone health interventions (including calcium and vitamin D supplementation, weightbearing exercise and bisphosphonate therapy) and factor replacement strategies may affect fracture rates. The findings of increased fracture risk with increasing severity of hemophilia coupled with the evidence for bleeding-independent mechanisms of decreased skeletal health suggested factor replacement may directly impact bone health and fracture risk in PWH.
Strauss et al [20]	2016	These authors evaluated the perioperative management and outcome in PWH following fracture fixation compared to a matched non-hemophilic control group. A cohort of 44 PWH who underwent 46 surgical fracture fixations was retrospectively compared to 46 nonhemophilic patients (matched-pair controls). Patients were classified according to the fracture localization: (i) proximal upper extremity (PrUEx; N = 7), (ii) distal upper extremity (DiUEx; N = 12), (iii) proximal lower extremity (PrLEx; N = 13) and (iv) distal lower extremity (DiLEx; N = 14). Both groups were assessed for length of hospital stay, duration of surgery, drainage use and complication rates.	There was no significant difference regarding the duration of the preoperative hospital stay between PWH and controls. Only PWH who were operated at the DiUEx stayed significantly longer in hospital (4.8 days) than controls (2.2 days; p = 0.039). Operation time was significantly longer in PWH with fractures treated at the DiLEx (64.9 minutes) compared to the controls (49.8 minutes; p = 0.035). Neither frequency nor duration of surgical drainage placement differed significantly between the two groups. The overall complication rate in both groups was low without a statistically significant difference.	An optimal interdisciplinary perioperative management provided the surgical treatment of fractures in PWH can be performed safely with a low complication rate.

Table 1. Continued

Reynolds et al [21]	2017	These authors presented a case of forearm compartment syndrome in a patient with mild hemophilia B who sustained an olecranon fracture. The patient received factor replacement and he underwent emergent forearm fasciotomies to avoid muscle necrosis.	Over the subsequent week, the patient returned to the operating room 3 times for repeat irrigation and debridements, partial wound closure, open reduction internal fixation of his olecranon fracture and eventual skin grafting of the volar forearm wound.	Failure to recognize compartment syndrome in even mild forms of hemophilia may result in loss of function, neurologic deficits, and limb amputations. The management of acute compartment syndrome in patients with hemophilia requires timely recognition, replacement of clotting factors, and emergent fasciotomies.
Tuan et al [22]	2019	These authors explored the relationship between hemophilia and the development of osteoporotic fractures following hemophilia. This was a nationwide population-based cohort study based on the data in the Taiwan National Health Insurance Research Database (TNHIRD). Patients who were diagnosed with hemophilia were selected. A comparison cohort was formed of patients without hemophilia who were matched according to age and sex. The incidence rate and the hazard ratios of new-onset osteoporotic fractures were calculated for both cohorts.	The hemophilia cohort consisted of 75 patients, and the comparison cohort comprised 300 matched control patients without hemophilia. The risk of osteoporotic fractures was higher in the hemophilia cohort than in the comparison cohort. After adjustments for age, sex, comorbidities, urbanizations and socio-economic status, PWH were 4.37 times more likely to develop osteoporotic fractures as compared to matched cohort. In addition, the incidence of newly diagnosed osteoporotic fractures was significantly increased after 5-year follow-up durations.	Though our study by TNHIRD presented methodologic flaws by its design nature, we observed that hemophilia may increase the risk of osteoporotic fractures and the cumulative incidence was significantly higher for PWH diagnosed more than 5 years. Clinicians should pay particular attention to osteoporotic fractures following hemophilia in PWH as they age.
Chen et al [23]	2021	Hemophilic pseudotumor (HPT)-related fracture is a rare but severe complication in patients with HPTs. These fractures often occur in femurs. There is no consensus on the standard surgical protocol for HPT-related femoral fracture. The present retrospective study evaluated the outcomes of these patients treated with surgical interventions. Ten patients with HPT-related femoral fractures who were treated with 14 surgical procedures due to 11 fractures in our hospital from January 2014 to April 2020 were evaluated retrospectively. Demographic data, fracture location, complications after surgery, and follow-up outcomes were recorded and analyzed. The mean follow-up period was 39.7 months.	The mean age at surgery was 31 years. Closed reduction external fixation (CREF) was originally performed in 2 patients, open reduction internal fixation (ORIF) was performed in 4 patients, screw fixation alone was performed in 1 patient, brace immobilization was performed in 1 patient, and amputation was performed in 3 patients. Bone union was observed in 5 patients, and an adequate callus was visible in 2 patients. Both patients with CREF had pin infections. Nonunion combined with external fixation (EF) failure occurred in 1 patient, and the plate was broken after ORIF. Three patients underwent autogenous or allogeneic cortical strut grafting. Three patients had HPT recurrence.	It is necessary to perform surgery in patients with HPT-related femoral fractures. Surgical treatments must consider fracture stabilization and HPT resection. Internal fixation is preferable, and EF should only be used for temporary fixation. If the HPT erodes more than one third of the bone diameter, strut grafts are necessary for mechanical stability. Amputation is an appropriate curative method in certain situations.
Pai et al [24]	2022	The world is aging, and hemophilia patients are as well. The association between PWH and low bone mineral density is clear. However, the incidence of fractures in patients with hemophilia is inconclusive, and no research has yet explored repeated fractures among PWH. In this study, we investigated the incidence of all-site fractures, repeated fractures and osteoporotic fractures amongst PWH. The study compared the incidence of all-site fractures, repeated fractures and osteoporotic fractures occurring in all PWH who were enrolled in Taiwan's National Health Insurance Research Database between 1997 and 2013 with an age- and gender-matched group from the general population. Eight-hundred thirty-two PWH, along with 8320 members of the general population, were included in the final analysis.	After multivariate Cox regression analysis with an adjustment for confounding factors, it was found that PWH experienced a higher risk of osteoporotic fracture but only saw a neutral effect with regards to both all-sites of fracture and repeated fractures, when compared with the general population. This 14-year population-based cohort study showed that PWH had a higher risk of osteoporotic fracture, but that hemophilia only had a neutral effect in all-sites of fracture and repeated fractures.	Screening, prevention and treatment for osteoporosis and further osteoporotic fractures among PWH, in order to improve quality of life and achieve healthy aging in this particular population, remain essential.
Alito et al [25]	2023	The incidence of some comorbidities, including fragility fractures, has increased in PWH. The aim of our research was to perform a review of the literature investigating the pathogenesis and multidisciplinary management of fractures in PWH. The PubMed, Scopus and Cochrane Library databases were searched to identify original research articles, meta-analyses, and scientific reviews on fragility fractures in PWH.	The mechanism underlying bone loss in PWH is multifactorial and includes recurrent joint bleeding, reduced physical activity with consequent reduction in mechanical load, nutritional deficiencies (particularly vitamin D), and factor VIII and factor IX deficiency. Pharmacological treatment of fractures in PWH includes antiresorptive, anabolic and dual action drugs. When conservative management is not possible, surgery is the preferred option, particularly in severe arthropathy, and rehabilitation is a key component in restoring function and maintaining mobility.	Appropriate multidisciplinary fracture management and an adapted and tailored rehabilitation pathway are essential to improve the quality of life of PWH and prevent long-term complications. Further clinical trials are needed to improve the management of fractures in PWH.

Table 1. Continued

Ransmann et al [26]	2024	This prospective cohort study aimed to assess the impact of hemophilia severity on BMD and to investigate trabecular bone score (TBS) and FRAX tool. This prospective cohort study evaluated the BMD, TBS, and FRAX in 255 persons with hemophilia using dual x-ray absorptiometry. The International Society for Clinical Densitometry guidelines were used for classification: osteoporosis (T-score <-2.5), osteopenia (T-score <-1.0), normal (T-score >-1.0). Patients younger than 50 years of age with a Z-score of <-2.0 were considered below the expected range for age.	Of 255 persons with hemophilia (mild: N = 52, moderate: N = 53, severe: N = 150) aged 43 years, 63.1% showed reduced BMD. Even 11.9% of persons with hemophilia aged <50 years were classified as below the expected range for age. Neck BMD decreased linearly with severity (mild: 0.907, moderate: 0.867, severe: 0.799; p = 0.01). TBS was classified as "normal" in n = 178 (81.3%) with a mean value of 1.403, and there were no differences between severity levels (p = 0.54). The FRAX was 4.4%. After adjustment of TBS, it was 2.8%.	This study showed that BMD was decreased in 63.1% of persons with hemophilia also depending on the severity of hemophilia. However, the largely normal TBS implied that the microarchitecture of the bone did not seem to be affected. It was recommended to include osteoporosis screening, including TBS analysis, in the comprehensive diagnostic work-up of persons with hemophilia, especially as they age.

BMD = bone mineral density; APCC = activated prothrombin complex concentrates; FRAX = fracture risk assessment.

Main body

Epidemiology of fractures

According to Gay et al (2015) the fracture prevalence in PWH was considerably higher, at 24.8 fractures per 1000 patient-years, than in the normal individuals, at 9.6 fractures per 1000 patient-years.[19]

Prevention of fractures

It is very important to prevent bone fractures in PWH, since their surgical treatment is associated with a high risk of bleeding if adequate hemostasis is not achieved. In 2013 Anagnostis et al stated that PWH had a low BMD (bone mineral density) and therefore a high risk of fractures.[13] In 2015 Anagnostis et al stated that the FRAX (fracture risk assessment) tool might be useful in PWH, for the reckoning of fracture risk.[17]

In 2019 Tuan et al affirmed that hemophilia might increase the risk of osteoporotic fractures.[22] In a 14-year population-based cohort study Pai et al (2022) found that PWH had a higher risk of osteoporotic fracture.[24]

In 2024 Ransmann et al found that BMD was reduced in 63.1% of PWH. Therefore, they advised to include osteoporosis screening in the diagnostic work-up of PWH, especially as they age.[26]

Treatment of fractures in PWH

In 1976 Boni and Ceciliani stated that if fractures in PWH are managed promptly and properly both from a hematological and orthopedic viewpoint, the outcomes are similar to those in normal individuals.[3] In 2002 Rodriguez-Merchan affirmed that if a fracture is properly managed in PWH, it will heal in a similar time-frame to fractures happening in normal individuals [Figures 1 and 2].[10]

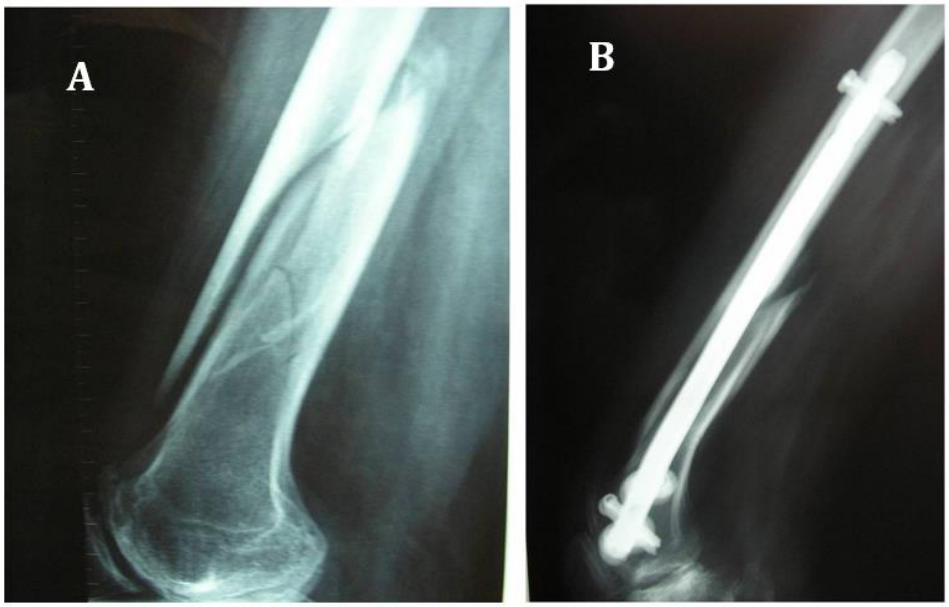

Figure 1 (A-B). Femoral fracture in a hemophilic patient treated by locked intramedullary nailing: (A) Preoperative radiograph; (B) Postoperative view

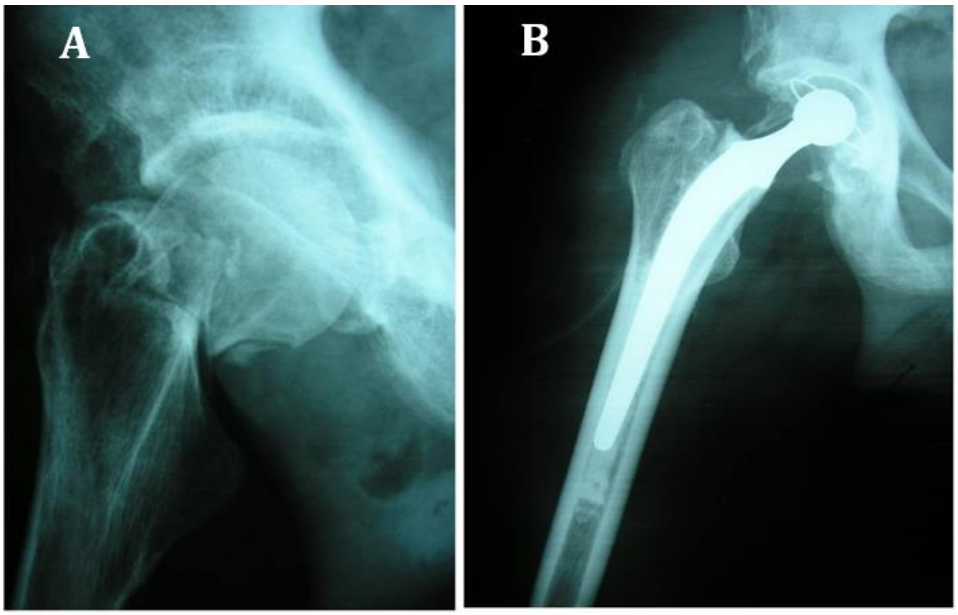

Figure 2 (A-B). Displaced fracture of the femoral neck in a hemophilic patient treated with total hip arthroplasty: (A) Preoperative view; (B) Postoperative radiograph

Lee et al (2007) stated that treatment of a fracture of the femoral neck in PWH was no different from normal individuals if an appropriate hemostasis is accomplished.[9] In 2015 Lin et al stated that external fixators can be utilized safely in treatment of open fractures of tibia and fibula in PWH A.[14]

Huang et al (2015) reported that with perfect preoperative preparation based on replacement therapy of the deficient coagulation factor, surgical treatment of fractures in PWH was safe and fracture healing was good. However, the risk of poor wound healing was elevated.[15]

In 2016 Strauss et al compared a group of 44 PWH who experienced 46 surgical fracture fixations to a group of 46 nonhemophilic patients. PWH who were operated at the distal upper extremity stayed substantially longer in hospital (4.8 days) than controls (2.2 days). Operation time was substantially longer in PWH with fractures treated at the distal lower extremity (64.9 minutes) compared to the controls (49.8 minutes).[20]

In 2023 Alito et al reported that adequate multidisciplinary fracture treatment and an adapted and tailored rehabilitation are fundamental to improve the quality of life of PWH and avert long-run adverse events.[25]

Perioperative factor coverage

According to Boardman and English (1980) PWH requiring surgical management of bone fractures must be covered with the deficient factor to a level of 60% for 2 weeks.[5]

In 1982 Wolff and Lovrien reported that fractures in PWH should be managed with 25 units/kg/day of factor. Fractures of the upper extremity should be kept at this dose for 7 days; lower limb fractures should be managed with factor for 14 days. Orthopedic treatment should be the same as utilized for normal individuals.[6]

Markakis et al (1984) reported that hemophilia did not influence the bone healing process with the provided that a prompt and sufficient substitution of the missing coagulation factors is carried out.[7]

Pathological fractures due to pseudotumors

According to Ishiguro et al (1998) if the preoperative treatment is adequately performed, a limb salvage procedure for a pathological fracture due to a pseudotumor could be made with success.[8]

In 2021 Chen et al stated that it is necessary to carry out surgery in PWH with hemophilic pseudotumor-related femoral fractures. Surgical treatments must contemplate fracture stabilization and hemophilic pseudotumor removal. Internal fixation is preferred, and external fixation should only be utilized for interim fixation. Amputation is an adequate alternative in certain circumstances.[23]

Venous thromboembolism after fracture surgery

According to Pruthi et al (2000) following hip arthroplasty for a hip fracture in PWH and a family history of venous thromboembolism, preoperative screening for the existence of the factor V Arg506Gln mutation and other thrombophilias might be useful.[9] It is important to emphasize that this conclusion about venous thromboembolism after fracture surgery was based on a clinical case.

Acute compartment syndrome after fracture

In 2017 Reynolds et al presented a case of forearm compartment syndrome in a patient with mild hemophilia B who sustained an olecranon fracture. After factor replacement the patient experienced emergent forearm

fasciotomies to avert muscle necrosis. In the following week, the patient required new surgical procedures (irrigation and debridement, partial wound closure, open reduction internal fixation of his fracture and eventual skin grafting of the volar forearm wound). Failure to perceive compartment syndrome might lead to loss of function, neurologic deficits, and limb amputations. The treatment of acute compartment syndrome in PWH requires prompt identification, replacement of the deficient clotting factor, and emergent fasciotomy.[21]

A paper published in 2021 by Carulli et al in a journal not included in PubMed, 19 fractures in PWH were treated with satisfactory results in 16. Three patients presented symptoms or functional impairments at mid-term, needing further surgery. The conclusion of this article was that fractures in PWH are uncommon and their management requires close cooperation with hemophilia specialists. Through multidisciplinary treatment it is possible to manage these challenging conditions in a safe manner and with a low rate of complications.

Conclusion

Bone fractures in PWH should be treated in the same way as in healthy individuals but with perioperative hemostasis control through intravenous infusion of the deficient coagulation factor (factor VIII in hemophilia A, factor IX in hemophilia B) at appropriate doses and for the necessary duration [Table 2].[27,28]

Table 2. Recommendations for peak factor levels and duration of factor replacement in the surgical treatment of bone fractures in people with hemophilia (PWH).[27,28]

	HEMOPHILIA A	HEMOPHILIA B
Preoperative peak factor activity objective	80%-100%	60%-80%
Postoperative peak factor activity objective	60%-80% (days 1-3) 40%-60% (days 4-6) 30%-50% (days 7-14)	40%-60% (days 1-3) 30%-50% (days 4-6) 20%-40% (days 7-14)

The number of fractures in PWH is not so high, despite the instrumental evidence of osteopenia/osteoporosis since their young ages.

In a paper published in 2021 by Carulli et al in a journal not included in PubMed, 19 fractures in PWH were treated with satisfactory results in sixteen. Three patients presented symptoms or functional impairments at mid-run, requiring further surgery. The conclusion of this article was that fractures in PWH were uncommon and their management required close cooperation with hemophilia specialists. Through multidisciplinary treatment it was possible to manage fractures in PWH in a safe manner and with a low rate of complications.[29]

Acknowledgement

N/A

Authors Contribution: Author who conceived and designed the analysis, collected the data, contributed data or analysis tools, performed the analysis and wrote the paper: E. Carlos Rodriguez-Merchan

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 "In Brief" review articles.

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.

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