Bone metabolism and fracture risk in haemophilia: a narrative review

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ABSTRACT

Purpose: Haemophilia is a rare inherited X-linked bleeding disorder caused by deficient levels of coagulative factor VIII (type A) or IX (type B). Deficiency of these factors may interfere with specific biochemical pathways, leading to increased bone resorption and decreased bone production.

To limit severe complications, fractures in patients with hemophilia should be managed by dedicated teams, from the emergency room to the operating theatre when surgery is indicated. The authors set out to analyze the recent literature on haemophilia, impaired bone metabolism, and fracture risk.

Methods: A narrative review was conducted, searching electronic databases for relevant articles and books published over the past two decades.

Results: 71 articles and book chapters were identified by title and abstract. Of these, 37 original articles and three book chapters met the inclusion and exclusion criteria.

Conclusions: Patients with haemophilia have impaired bone metabolism, particularly when haematological treatment is on-demand or prophylaxis is initiated late. To date, however, this impaired bone metabolism has not been shown to increase fracture frequency.

KEYWORDS

Haemophilia, bone metabolism, osteopenia, osteoporosis, arthropathy, joint replacement, fracture, prophylaxis.

Introduction

Haemophilia is a rare congenital disease, manifesting as recurrent bleeding episodes due to deficiency of coagulative factor VIII (haemophilia A) or IX (haemophilia B). Until a few decades ago, it was a life-threatening disease, particularly when bleeding affected vital organs; however, modern haematological prophylaxis, based on periodic infusions of deficient factors starting in childhood, has dramatically reduced the mortality and morbidity of haemophilia, improving patients' life expectancy and quality of life [1,2]. Despite these crucial steps forward, hemophilia is still associated with musculoskeletal changes, which constitute its most common complications [3]. The initial manifestations are usually muscle haematoma and hemarthrosis, associated with early onset of pain and functional impairment. While muscle bleeds usually resolve spontaneously within a few days, joint hemorrhages are prone to lead to synovitis. Recurrent bleeds can induce persistent synovitis which, when chronic, can evolve into so-called haemophilic arthropathy [4]. The knees, ankles, elbows, and less frequently hips, shoulders, and wrists are commonly affected [5-7]. An arthropathic joint is characterized by pain, loss of function and muscle tone, and progression to severe secondary arthritis at very early ages. Thus, individuals with hemophilia need to be periodically monitored by multidisciplinary/multiprofessional teams, and in particular by a musculoskeletal expert. They often require orthopedic treatments, ranging from medical treatments and conservative approaches to surgical procedures [8-13]. Like the non-haemorrhagic population, people with haemophilia may experience trauma and falls, sometimes resulting in fractures. Over the past decade, research has focused on impaired bone metabolism in people with haemophilia, which tends to arise earlier in this population as a consequence of joint arthropathy [14,15]. It has been postulated that factor VIII and IX deficiencies may affect specific biochemical pathways, leading to increased bone resorption and decreased bone formation [16]. Osteopenia/osteoporosis needs to be addressed early, first through the introduction of hematological prophylaxis, then by preventing chronic synovitis and arthropathy, and finally by implementing all appropriate strategies to improve bone metabolism: an active lifestyle, an adequate diet, and oral supplementation of calcium and vitamin D [17]. Fractures in individuals with haemophilia

Article history
Received 5 Nov 2025 – Accepted 19 Nov 2025

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should be managed by dedicated teams, from the emergency room to the operating theatre when surgery is indicated, in order to limit severe complications (hemorrhages, compartment syndrome). In the 1980s and 1990s, many patients with haemophilia underwent joint replacement at very young ages. In these patients—as in the general population—periprosthetic fractures have increased in recent years, and such fractures require tailored management by specialized teams [14,15]. Despite all the above-mentioned considerations and the higher risk of osteoporosis in haemophilia, the fracture rate in this population remains relatively low—an aspect that needs to be clarified. That said, these events appear to be more prevalent in patients not receiving primary or secondary prophylaxis [18].

In recent years, dual-energy X-ray absorptiometry (DEXA) has revealed a pattern of decreased bone mineral density (BMD) and osteoporosis in individuals with haemophilia [19-21]. In this context, the growing participation of affected individuals in physical activities and sports has both positive and negative implications: while physical activity provides natural beneficial stimulation for bone health, it also increases the risk of traumatic injury [22,23]. It is well established that haematological prophylaxis supports more favorable bone metabolism, through the interaction of biomarkers like osteoprotegerin, the RANK–RANKL complex, and IL-10 [24,25].

The present analysis is a narrative review of the recent literature on this topic.

Methods

A narrative review was conducted focusing on papers dealing with bone metabolism alterations in haemophilia and also reporting the prevalence of fractures in this population of patients. The electronic databases MEDLINE, EMBASE, and Cochrane were reviewed: they were examined for relevant articles, which had to have been published in English within the two decades ending at the start of 2025. The following search terms were used: haemophilia, bone metabolism, osteopenia, osteoporosis, synovitis, arthropathy, joint replacement, fracture, and prophylaxis. The inclusion criteria were articles, case series, trials, book chapters, and *in vitro* studies addressing the topic and containing the keywords mentioned above. Exclusion criteria were expert opinions, letters to the editor, duplicated papers (identified using Zotero software, Roy Rosenzweig Center for History and New Media, 2016), sources written in languages other than English, and studies whose full text was not obtained.

Results

The initial search across the mentioned databases yielded found 213 sources. After application of the exclusion criteria, 71 articles and book chapters were screened by title and abstract. The final selection comprised 37 original articles and three book chapters that fully met both the inclusion and exclusion criteria and were therefore included in the narrative review.

Discussion

Haemophilia is now a less risky disease than it was even in the recent past, and affected individuals in many countries can therefore enjoy a better quality of life. Fractures can be challenging to be treat, particularly if they involve severe displacement, exposed bones, and periprosthetic patterns. As in individuals with a normal coagulation cascade, non-displaced fractures are not now a critical issue in patients with haemophilia. On the other hand, complicated fractures, subjects with specific types of haemophilia (mostly, type A and patients with inhibitors), or on other treatments (anticoagulant therapies) should be managed in dedicated facilities [14,15]. Displaced fractures, as well as long-bone or periprosthetic fractures, may carry a high risk of bleeding and postoperative infection. In these cases, immediate or urgent management by an expert team is required. Perioperative tailored haematologic regimens with FVIII or IX concentrates and early rehabilitation protocols are mandatory to obtain efficient bleeding control, healing of the fracture, and adequate functional recovery [15,17].

However, despite recent evidence of a very high risk of osteopenia and osteoporosis, fractures in individuals with hemophilia are not common. Nonetheless, decreased BMD, along with muscle hypotrophy, joint stiffness, and joint malalignment are undeniable issues [18,26].

Modern prophylaxis has undoubtedly improved these patients' quality of life by allowing them to participate in a greater range of activities and sports; moreover, no correlation between increased activity and number of fractures has been established. From a technical standpoint, a fracture occurring in an arthropathic and/or misaligned joint may require special attention, as treatment may involve not only addressing the fracture, but also stabilizing and managing the joint itself. A particular emerging problem is the periprosthetic fracture, which carries further risks in terms of intra/postoperative complications, and mid- to long-term functional limitations, given the high probability of loosening of the prosthetic components. The indications for surgical treatment of these fractures in individuals with hemophilia are generally the same as in other patients; however, in haemophilia, it is also necessary to consider variables such as advanced arthropathy, poor bone quality, limb malalignment, poor soft tissue condition) [27-29]. This review found that very few experiences have been reported in recent years, reflecting the fact that haemophilia is a rare disease. Surgery was associated with good outcomes, although there was an increased risk of major intra-/postoperative bleeding, wound healing complications, and postoperative infections.

Strauss and colleagues found no substantial difference in fracture management outcomes between haemophilic and non-haemophilic subjects when patients were followed by dedicated multidisciplinary teams [30].

Caviglia *et al*. reported the largest series of fractures in people with haemophilia published to date [18]. They managed 151 fractures in 141 patients (121 treated conservatively, the remainder with internal fixation). During follow-up, they found 40 cases of malalignment in the non-operated group, versus three cases in the operated group. Moreover, the patients treated with internal fixation showed shorter fracture consolidation times and better anatomical alignment than those receiving conservative treatment. The number of fractures was higher in the historical period of on-demand haematological prophylaxis than subsequently, when primary/secondary prophylaxis became standard.

Ghosh and colleagues reported a series of 20 cases of fractures in patients with haemophilia [31], none of whom was on a prophylactic factor replacement regimen. In many of these patients, bleeding was treated by symptomatic measures, such as immobilization, ice application, and analgesics. Bone density assessment by DEXA was performed in six cases. Osteoporosis of the lumbar spine was found in all the patients, and osteoporosis of the hips in two (four patients had osteopenia). The average fracture healing time was 6.5 months (4–18 months), much higher than in healthy individuals with the same fracture.

Gallacher *et al*. found a mean Z-score of -0.92 in children with severe haemophilia, confirming that early weight-bearing exercises are crucial for the development of adequate bone mass in childhood [19].

Carulli *et al*. reported a series of 19 fractures in haemophilia patients: 15 were receiving prophylaxis with clotting or recombinant factors at the time of trauma, and four were on “on-demand” treatment. Sixteen were lower limb and three upper limb fractures. In all cases, surgery was performed by the same orthopedic team, without postoperative complications, major bleeding, or instances of deep vein thrombosis [15].

Sossa Melo *et al*. studied 90 patients with haemophilia A and B studied by DEXA and the Global Physical Activity questionnaire. They found haemophilia to be associated with a higher frequency of low BMD and with elevated C-reactive protein levels [32].

Strauss *et al*. retrospectively evaluated 33 adult subjects with haemophilia, identifying seven cases of osteoporosis and 16 of osteopenia. Bone density, reduced at presentation, remained stable at low levels during follow-up. Moreover, vitamin D deficiency and joint alterations emerged as further risk factors for osteoporosis [33].

Rodriguez-Merchan explored the importance of osteoporosis prevention in haemophilia, which should include primary haematological prophylaxis, adequate calcium and vitamin D intake, regular exercise programs, including aerobic, strength, and flexibility training, restriction of tobacco and alcohol use, and limitation of immobilization [34].

Anagnostis *et al*. studied the effect of monthly ibandronate on BMD and bone turnover markers in patients with haemophilia A and B and found that ibandronate significantly improved BMD at the lumbar spine and reduced bone resorption in adults with haemophilia A or B at increased risk of fracture; however, its effect on hip BMD and bone formation markers was not significant [35].

Parhampour *et al*. found that in patients with severe haemophilia A and osteoporosis, short-term resistance training significantly improved bone metabolism by increasing bone-specific alkaline phosphatase [36].

Suggestions to advance knowledge of bone metabolism alterations in subjects with haemorrhagic diseases, to allow better assessment of the objective need for pharmacological interventions for osteoporosis, have also been offered by Petkovic and colleagues [37].

Kovacs observed that young patients (<50 years) treated with antiresorptive bisphosphonates achieved low peak bone mass, whereas adequate levels were reached in the few subjects with previous fragility fractures and in those showing rapid loss of bone mass on sequential BMD measurements [38].

Wu and Shen reported a series of 53 patients with severe haemophilia type A compared with 49 healthy participants. DEXA analysis revealed much lower bone density in the former group, most notably in the hips. They postulated that low body mass index and progressive functional impairments were the main risk factors [39].

Ulivieri *et al*. evaluated BMD, Trabecular Bone Score (TBS), bone strain (BS), and hip structural analysis (HSA) in 70 adults with haemophilia and correlated these measures with both general and specific risk factors for osteoporosis, as well as with the Hemophilia Joint Health Score (HJHS). All data derived from the lumbar spine and femur were analyzed. Lower BMD and altered HSA correlated with HJHS, whereas TBS did not appear to be influenced by hemophilic arthropathy [40].

The present narrative review has some limitations. The number of clinical series and reported experiences was small, making statistical analysis difficult, and haematological prophylaxis varied considerably across continents and countries with different levels of economic development. Finally, the actual number of fractures was low, contrasting with several benchmark studies that point to a high prevalence of osteoporosis and an elevated risk of fractures in haemophilia [20,22,31].

Conclusions

Subjects with haemophilia show early alterations in bone metabolism, particularly when haematological treatment is on-demand or prophylaxis is initiated late. To date, however, hemophilia has not been associated with an increased fracture rate. Further studies on bone density in these patients are needed to better understand this phenomenon. In any case, early implementation of pharmacological and non-pharmacological strategies is warranted in this population.

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