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REVIEW ARTICLE

Osteoporosis management and falls prevention in patients with haemophilia: Review of haemophilia guidelines

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Abstract

Introduction: Patients with haemophilia (PWH) have a high prevalence of osteoporosis, falls and fractures at all ages. The role of haemophilia itself may contribute to low bone mineral density (BMD) due to coagulation factor deficiency. Guidelines for the management of osteoporosis, fracture and fall risk may help to reduce fracture and fall risk, and delay osteoporosis onset.

Aim: We aim to review current haemophilia guidelines regarding osteoporosis prevention, screening, diagnosis and management, and fall prevention.

Method: A database search (Ovid MEDLINE) revealed two haemophilia guidelines (World and British) published within the last ten years. Local Australian haemophilia guidelines were identified through a manual search.

Results: All haemophilia guidelines were found to contain inadequate recommendations for osteoporosis management and fall prevention due to a lack of evidence in the literature.

Conclusion: Further studies are required to assess the trajectory of bone health in PWH, the mechanism of bone loss in PWH, and the effectiveness of weight-bearing exercises, interventions for fall prevention, screening programmes, and use of anti-osteoporosis medications in PWH across the lifecourse.

KEYWORDS
bone mineral density, fall, fracture, guideline, haemophilia, osteoporosis

1 | INTRODUCTION

Haemophilia is an X-linked recessive bleeding disorder, primarily affecting men. Disease severity is based on circulating factor levels with 6–40%, 1–5% or < 1% corresponding to mild, moderate or severe disease, respectively.[1] Coagulation factor deficiency results in impaired thrombus formation leaving patients prone to recurrent spontaneous bleeding, with 70–80% of bleeds occurring in joints and 10–20% of bleeds occurring in muscles.[2] This commonly leads to chronic musculoskeletal complications, such as haemophilic arthropathy, which impairs mobility.[3] Standard treatment involves regular prophylactic intravenous infusions of factor concentrates. A monoclonal antibody, emicizumab (administered subcutaneously), is now also available for treatment in patients with haemophilia A.[4] The HAVEN3 and HAVEN4 studies showed that treatment with emicizumab produced clinically significant improvements in haemophilia-specific quality of life in 54% of patients (n = 176), which were maintained through to 73 weeks.[4] These improvements were related to better bleed control.[4]

Advancements in treatment have improved the quality of life and extended the life expectancy of PWH, now similar to the general population. As such, it is important for clinicians to focus on musculoskeletal comorbidities of ageing, such as osteoporosis, highly prevalent in PWH.[5]

Osteoporosis is a condition of reduced bone mineral density (BMD) and altered microarchitecture, which increases bone fragility.[5] Consequently, patients with osteoporosis are prone to minimal trauma fractures, such as, after a fall from a standing height.[5] BMD is assessed using dual-energy x-ray absorptiometry (DXA) with T-scores comparing BMD at the femoral neck, total hip and lumbar spine against the average peak bone mass of young, healthy adults at age 30 years.[6] Osteopenia is defined as a T-score between -1 to -2.5 standard deviations (SD) and osteoporosis as a T-score $\leq$ -2.5.[6] A Z-score is recommended for age-and sex-matched comparisons in patients younger than age 50 years[7]; for instance, Z-score $\leq$ 2 in children is diagnosed as low bone mass for age.[5] Osteoporosis is diagnosed in adults aged $<$ 50 years, if there has been a minimal trauma fracture or low BMD (Z-score $\leq$ 2) in the presence of clinical risk factors for osteoporosis.[5]

There is a strong association between haemophilia and low BMD across all ages. Studies in PWH have shown 27–28% of adults have low BMD (mean age 45.9 years, 95% on-demand therapy, 5% prophylactic therapy),[8,9] while another study reported low BMD in 69.5% in those with a mean age of 41 years (factor replacement therapy status unknown).[10] Consistent with data in adults, children with haemophilia also have low BMD, with two meta-analyses reporting that these changes commenced in early childhood.[11–14]

Multiple factors may contribute to low bone mass in haemophilia, including reduced height and weight, reduced physical activity, haemophilic arthropathy, muscle atrophy, hepatitis C infection, human immunodeficiency virus (HIV) infection and vitamin D deficiency.[7,10,15,16] However, animal models of haemophilia suggest that low BMD may also be independent of these factors, related to coagulation factor deficiency itself.[17,18] Factor VIII knockout mice have reduced femoral BMD and cortical bone thickness demonstrated by DXA and micro-computed tomography (micro-CT).[18] Additionally, factor VIII knockout mice have decreased trabecular density and bone area with increased osteoclasts lining the bone perimeter on histomorphometry, and supports increased bone resorption as the process of bone loss.[17] Together, these mouse models indicate a direct effect of factor VIII on bone remodelling and prophylactic factor replacement therapy could potentially prevent osteoporosis in PWH.

Thrombin and the receptor activator of nuclear factor kappa-B (RANK)/RANK ligand (RANKL)/osteoprotegerin (OPG) pathway may play a key role in the molecular mechanisms of bone remodelling in haemophilia. In addition to its primary role in haemostasis, thrombin has non-haemostatic functions with evidence suggesting factor VIII and factor IX deficiency have an indirect effect on bone metabolism by reducing thrombin generation.[19] Protease-activated receptor 1 (PAR-1) is found on osteoblasts and when activated by thrombin it induces proliferation.[20] These findings indicate that reduced thrombin generation in PWH may reduce osteoblast number leading to reduced bone formation. Factor VIII and PAR knockout mice have been shown to have reduced BMD (micro-CT analysis) and altered trabecular bone structure (histomorphometry),[21] highlighting the importance of the factor VIII/thrombin/PAR1 axis in bone remodelling. Furthermore, the factor VIII-vWF (von Willebrand factor) complex inhibits RANKL-induced osteoclastogenesis by binding to RANKL and also by increasing the affinity of OPG to RANKL; both reduce the binding of RANKL to RANK, thereby inhibiting osteoclastogenesis.[22] Consequently, PWH with lower level suppression have higher osteoclastogenesis and bone resorption, explaining the increase in the RANK and RANKL/OPG ratio.[9]

Given the reported low BMD in PWH, there is a subsequent increased fracture risk. A 10-year retrospective cohort study of 382 men with haemophilia found that PWH have a higher prevalence of fractures compared with the general population (24.8 vs 9.6 fractures per 1000 patient-years, mean age 23 years, factor replacement therapy status unknown).[23] Likewise, a population-based cohort study ($n = 75$, mean age 35.7 years, factor replacement therapy status unknown) found that PWH are at 4.37 times greater risk of osteoporotic fractures than controls.[24] The fracture prevalence in PWH is reported to range from 4% to 37%,[25] with one study reporting the combined prevalence of hip, vertebral and peripheral skeleton fractures as 16% in PWH ($n = 104$, mean age 45.9 years)[8] – significantly higher than the 0.1% fracture prevalence found in the general population of a similar age from the same region.[26] In the general population, hip fractures in older adults have a high mortality, with 15% of patients dying during their initial hospital presentation and one third not surviving past 1-year post-fracture.[27] Additionally, fractures in PWH have a high morbidity as they further limit mobility and weight-bearing capacity, contributing to further declines in BMD.

Given the low BMD and increased fracture prevalence in PWH, it is important for physicians to screen, diagnose and treat these patients for osteoporosis. Fall prevention is also important, as falls are the main cause of minimal trauma fractures. We aim to review the most recent haemophilia guidelines regarding the musculoskeletal management of patient care.

2 | METHODS

A search was performed using Ovid MEDLINE to identify the most current haemophilia guidelines, limiting to the past 10 years (from 2011 onwards). The keyword hemophilia/haemophilia was searched in addition to guideline*. This search returned 320 results. Titles and abstracts were screened to identify relevant articles. Inclusion criteria included recent general haemophilia guidelines from any country in the English language (or English translation) containing a section on osteoporosis and/or fall prevention. The exclusion criteria included original research articles, review articles, meta-analyses, letters to the editor and editorials and disease irrelevance (von Willebrand disease, acquired haemophilia A). A manual web search of relevant haemophilia

organisations was conducted where the National Blood Authority Australia, Haemophilia Foundation Australia, Australian Haemophilia Centre Directors' Organisation were identified and reviewed. Our search yielded three guidelines: 2020 British,[28] 2020 World Federation of Haemophilia (WFH)[2] and 2016 Australian Haemophilia Guidelines.[29]

To identify relevant sections in the haemophilia guidelines, search terms pertaining to osteoporosis prevention, screening, diagnosis, treatment and fall prevention were searched. Relevant sections in the WFH guidelines were Chapters 1.10, 2.2, 2.3, 2.4, 2.6, 7.2, 9.8 and 10.[2] Key sections in the Australian guidelines were Chapters 1.4, 2.7 and 6.1, Sections 1.5.3, 1.8.3, 5.2.14, 6.1.60 and 6.1.62 and practice points 1.8, 5.5, 6.1, 6.2 and 6.3.[29] Relevant sections in the British guidelines were musculoskeletal health, physical examination, health promotion and optimisation of bone and joint health.[28]

3 | RESULTS AND DISCUSSION

3.1 | Osteoporosis screening and diagnosis

The WFH guidelines remark on uncertainty surrounding whether all PWH need routine screening for osteoporosis. However, the guidelines do suggest that screening may be appropriate in PWH who are at high risk or have multiple clinical risk factors for osteoporosis.[2] British guidelines only recommend regular osteoporosis screening for PWH on antiretrovirals and state that the fracture risk assessment tool (FRAX®) can be used for guidance.[28] Australian guidelines state that all PWH should be screened according to the local guidelines for osteoporosis.[29] The local Australian osteoporosis guidelines state that an osteoporosis risk assessment should be conducted in postmenopausal women and men aged > 50 years with at least one major risk factor for minimal trauma fractures.[30] Patients deemed to be at high risk should proceed to a DXA scan for screening and diagnosis. DXA scans should also be conducted in patients over 70 years of age, with a minimal trauma fracture or < 50 years of age with a disease known to cause low BMD.[30]

Haemophilia is not a widely recognised secondary cause of osteoporosis.[31] As such, osteoporosis is not screened routinely in PWH. While haemophilia is a relatively rare condition, there is a high prevalence of low BMD (27-69.5%)[8–10] and fracture (4-37%),[25] which is comparable to the prevalence of widely recognised risk factors including hyperthyroidism (63% low BMD, 35% vertebral fracture)[32] coeliac disease (49% low BMD, 25% peripheral skeleton fracture)[33,34] and rheumatoid arthritis (20% low BMD, 36% vertebral fracture).[35,36] This suggests that routine osteoporosis screening may be appropriate for certain groups of PWH (disease severity, adherence and type of prophylaxis, and age); data from the PHILEOS Study will inform on which group of PWH will benefit most from osteoporosis screening.[37]

The majority of fractures within the general population occur in those aged over 65 years[24]; in contrast, the majority of fractures in PWH occur much earlier, with 81% occurring below the age of 50 years (factor replacement therapy status unknown),[38] and 23–75% occurring below the age of 35–36 years (factor replacement therapy status unknown).[24,39] Minimal trauma fractures have also been reported in children with haemophilia, with one study reporting 4 out of 22 fractures occurring in children aged 14 and 15 years who had on demand therapy.[39] The average age of fracture in PWH is 28–30 years,[8,25,38,39] which is considerably younger than in the general population, where the average age is approximately 76 years.[40] Although, PWH aged ≥31 years are twice as likely to sustain a fracture compared with PWH aged ≤30years (RR = 2.15, $P = 0.0047$).[23] Concerningly, the haemophilia population is under-screened with a study finding that 92% of PWH were diagnosed with osteoporosis at the same time they were diagnosed with fracture (factor replacement therapy status unknown).[24]

There is no consensus as to what age osteoporosis screening should take place in PWH, with studies suggesting screening in childhood,[15,41] early adulthood,[16,42] > 40 years[43] and > 50 years of age, unless clinical risk factors present earlier.[44] Notably, these recommendations are based on BMD and prevalence of fracture in PWH, as there are no longitudinal data on the utility and effectiveness of osteoporosis screening. The premature fractures occurring in PWH suggest that the Australian haemophilia guideline recommendation to follow local guidelines,[29] where screening starts at the age of 50 years, is inappropriate.

Evidence has shown that fracture prevalence increases with the severity of haemophilia,[8] as fracture risk is 44% higher in PWH who have severe compared with mild-moderate disease.[23] However, low BMD and fracture prevalence are still elevated in mild-moderate disease. Prophylactic factor replacement therapy may inhibit low BMD due to the intrinsic effects of coagulation factors on bone metabolism,[22] and the increased mobility from the reduction in bleed occurrence with treatment.[45,46] Thus, impaired bone health may be more significant in older PWH who predominantly received on-demand treatment or had delayed initiation of prophylactic therapy. While prophylaxis is now the standard treatment for PWH, this may not be the case in countries with limited resources.[47] Patients treated with on-demand factor replacement therapy versus prophylaxis have lower BMD measured by DXA,[43,48,49] although studies have also found no impact of prophylaxis on BMD in children and adolescents[50] and adults (mean age of prophylactic therapy initiation 31.3 years).[46] The data are inconclusive as many studies fail to disclose details of factor replacement therapy and studies use heterogeneous patient groups regarding age, disease severity, and onset, duration, frequency, and mode of factor replacement therapy.

The PHILEOS study is a multicentre prospective case-control study that aims to evaluate bone health in adult PWH who are categorised by prophylaxis status and age at treatment initiation.[37] PHILEOS will provide data on whether absence of prophylactic therapy, delay in therapy initiation and severe disease increase osteoporosis risk, necessitating selective screening.[37] In addition, The Haemophilia Osteoporosis Registry (THOR), will assess BMD and other components of bone strength using DXA and high resolution peripheral quantitative computed tomography (HR-pQCT) to identify the best window for bone density screening in PWH and what particular aspects of bone strength are compromised in this population.[51] Current haemophilia guidelines on osteoporosis screening and diagnosis are inadequate as there are

limited data available to provide evidence-based recommendations. Further research is required to determine what age would be most effective for screening and whether various risk factors should be considered.

3.2 | Calcium and vitamin D

There is general consensus across the haemophilia guidelines regarding routine prescription of calcium and vitamin D supplements for osteoporosis prevention. Adequate calcium and vitamin D intake is encouraged in the WFH guidelines,[2] while the Australian guidelines state that calcium and vitamin D supplements are only required for prevention when intake and exposure is inadequate.[29] The British guidelines do not recommend routine vitamin D supplements for osteoporosis prevention.[28]

The effect of vitamin D supplementation on fracture prevention in the general population has been controversial, with one of the main discrepancies being the difference in baseline vitamin D levels in study participants. One meta-analysis of 12 RCTs found that vitamin D supplementation (482-770 IU/day) reduced nonvertebral fractures by 20% in patients aged over 65 years with no additional effect from calcium supplementation; the mean baseline serum 25-hydroxyvitamin D (25OHD) levels in patients from eight of these RCTs ranged from 21.3 to 76.5 nmol/L, with vitamin D deficiency (mean 25OHD < 50 nmol/L) present in 75% of studies.[52] Conversely, a recent meta-analysis of 81 RCTs revealed that vitamin D supplementation does not improve BMD or prevent falls or fractures in a clinically meaningful way regardless of dose.[53] Out of the 72 included trials, 57% were in populations with vitamin D deficiency (mean 25OHD < 50 nmol/L).[53] The Vitamin D Assessment (ViDA) sub-study showed that vitamin D alone is better at increasing BMD only in patients with baseline vitamin D levels < 30 nmol/L.[54] Kempton et al.[5] suggest routine vitamin D screening in PWH, as low BMD is prevalent in this population.[8–10,55] However, data on the relationship between vitamin D deficiency and low BMD in PWH are conflicting. One study found that 47% of PWH had vitamin D deficiency (< 50 nmol/mL), with serum vitamin D levels predicting BMD at the total hip, femoral neck and greater trochanter.[8] Conversely, another study in PWH found no correlation between BMD and vitamin D despite vitamin D deficiency (< 50 nmol/L) in 77.5% of participants.[55] Further research is required to clarify associations between vitamin D and BMD in PWH.

3.3 | Osteoporosis treatment

The WFH guidelines state that anti-osteoporosis medication should be commenced in PWH with osteoporosis, minimal trauma fractures or high fracture risk.[2] Additionally, PWH with osteopenia should commence bisphosphonates if appropriate.[2] Australian guidelines state that bisphosphonates may be required in some PWH.[29] British guidelines do not advise on specific anti-osteoporosis medications.[28]

FRAX® is well supported for use in PWH aged > 40 years, to calculate absolute fracture risk and help guide treatment decisions.[5,42,43] However, FRAX® is not applicable in many PWH in whom BMD is a concern as they are much younger. Alternative risk calculators have not been developed for this younger age group, making determination of fracture risk and need for treatment difficult.

There are two categories of anti-osteoporosis medications currently being used for treatment (Table 1); none of these have been thoroughly assessed in PWH. Bisphosphonates and denosumab are antiresorptive medications that are used as first-line treatments for osteoporosis, while teriparatide is an anabolic agent that is used as a second-line therapy.[30] Romosozumab is a mixed anabolic and antiresorptive agent.[56] Denosumab is gaining popularity over oral bisphosphonates due to its six monthly subcutaneous administration and may be preferred in PWH due to the gastrointestinal bleeding risks associated with bisphosphonates, although rare.[57] This needs to be balanced against the possibility of increased bruising and bleeding from subcutaneous administration. Teriparatide is an anabolic agent, so often is reserved for patients who sustain a fracture on antiresorptive therapy, with a T-score ≤ 3 or with at least two fractures.[30] Anti-osteoporosis medications have been effective in improving BMD and subsequently mortality risk reduction.[58] It is yet to be assessed whether comparable treatment benefits are seen in PWH.

Treatment recommendations in the haemophilia guidelines are insufficient as there is only a single study that has assessed anti-osteoporosis treatment in PWH. This prospective study involved 10 PWH (mean age 43.5 years, 30% receiving prophylactic therapy) who received treatment with oral ibandronate (150 mg/month) for 12 months.[59] There was a 4.7% increase in BMD at the lumbar spine (.886 to .927 g/cm^2, $P = .004$) but no change at the total hip or femoral neck after 12 months.[59] Ibandronate also decreased serum concentrations of C-terminal telopeptide of type 1 collagen (CTX), a bone resorption marker.[59] Additionally, ibandronate use has been associated with reduced levels of dickkopf-related protein 1 (Dkk-1), an osteoblast inhibitor, which may indicate increased osteoblast activity and bone formation.[9] Together, these findings suggest that bisphosphonates may be an effective therapy in PWH and warrant further investigation with larger group sizes to ensure robust analyses.

The trajectory of bone mass accrual and loss in PWH is yet to be determined. It has been hypothesised that peak bone mass is not achieved in PWH and that accelerated bone loss occurs during the usual plateau period between 25 and 50 years of age.[7] Given this uncertainty, some have advised against antiresorptive treatment in PWH aged < 50 years unless there is evidence of serial bone loss on two sequential BMD measurements taken 18–24 months apart.[7,43] This is because antiresorptive medications act to combat excessive bone resorption that leads to bone fragility and may not be appropriate in the setting of isolated low peak bone mass where bone architecture may be normal.[7] While the concern arising from this approach is that delaying therapy initiation in young PWH may lead to minimal trauma fractures, primary prevention using pharmacological therapy in children prior to first fracture is not current practice due to insufficient research.[60] Monitoring BMD is a reasonable approach that enables early initiation of interventions including exercise, vitamin D optimisation and healthy weight promotion.[60] Further studies

TABLE 1 First and second-line anti-osteoporosis treatment

	Mode of delivery	Mechanism of action	Side effects
First-line antiresorptive agents			
Bisphosphonates	Daily or weekly oral alendronate or risedronate Once yearly intravenous zoledronic acid infusion[30]	Increase osteoclast apoptosis and prevents osteoclast progenitor development leading to reduced bone resorption[5]	Atypical femur fractures Osteonecrosis of the jaw Oesophageal erosions, strictures, gastric ulcers and perforations[30]
Denosumab	6 monthly subcutaneous injection[30]	Monoclonal antibody that suppresses RANKL which impairs osteoclast differentiation and survival leading to reduced bone resorption[5]	Cellulitis Hypocalcaemia in stage 4 or 5 chronic kidney disease[30]
Second-line anabolic or mixed agents			
Romosozumab	Monthly subcutaneous injections[56]	Mixed anabolic and antiresorptive agent. Monoclonal antibody that inhibits sclerostin, leading to increased bone formation through increased recruitment of osteoprogenitors and matrix production by osteoblasts. Bone resorption is also reduced through altered expression of osteoclast mediators[75]	Cardiovascular events Osteoarthritis Injection site reaction Hyperostosis Osteonecrosis of the jaw Atypical femur fractures[76]
Teriparatide	Daily subcutaneous injection[30]	Anabolic agent that causes osteoblast maturation and reduces osteoblast apoptosis leading to bone formation[30]	Injection site reaction Headache Nausea Dizziness Leg cramps[30] Osteogenic sarcoma in rats but not in humans (contraindicated in bone disease and malignancy)[77,78]

are needed to determine the bone mass profile in PWH across the lifecourse.

If treatment is to be implemented in young adults and potentially children, it is important for anti-osteoporosis medications to be safe and effective in this younger population. A 7-year retrospective study found that intravenous bisphosphonates (pamidronate and/or zoledronic acid) increased BMD at the lumbar spine in children with secondary osteoporosis but did not reduce fracture risk ($n = 46$, mean age at first infusion: 11.5 years).[61] The acute side effects were mild and infrequent (16% of infusions), including hypocalcaemia and hypophosphataemia, and no atypical femur fractures or osteonecrosis of the jaw were reported.[61] No studies have assessed anti-osteoporosis treatment in children with haemophilia to evaluate whether they are equally safe and effective. Investigating the most effective treatment in children with haemophilia is required to determine efficacy and safety.

Understanding the mechanism of low BMD in haemophilia is important for determining whether antiresorptive or anabolic therapy is likely to be most effective in PWH. Bone turnover markers have been assessed in human studies with conflicting results. Studies have revealed increased bone resorption with elevated parathyroid hormone and reduced OPG,[62,63] no change in bone resorption with unaltered CTX,[64] reduced bone formation with low osteocalcin,[21,63,64] and likely compensatory increased bone formation with high osteocalcin.[62] Taken together, evidence from human studies in PWH are in support of an increase in bone resorption and potentially a decrease in bone formation as the likely mechanism of low BMD in this population.

In support of these mechanisms in humans, preclinical mouse models have been utilised in haemophilia. Male factor VIII knockout mouse models revealed that reduced bone mass was due to increased bone resorption (increased osteoclast number).[17] There were no changes in bone formation (unchanged osteocalcin).[17] These findings are like the female factor VIII knockout mouse model, which showed increased bone resorption (increased CTX) that primarily affected cortical bone in the vertebrae and femur, with no change in bone formation [unchanged procollagen type 1 N-terminal propeptide (P1NP)].[65] In contrast, a male knockout mouse model from the same study showed reduced bone formation (reduced P1NP), that increased with age and primarily affected trabecular bone in the vertebrae and femur and vertebral cortical bone mass.[65] Unchanged CTX indicated no alteration in bone resorption.[65] This sexual dimorphism has clinical significance, as it suggests that males may benefit more from anabolic agents, while females benefit more from antiresorptive agents.[65] However, this finding has not been replicated in human studies and overall there is a greater consensus for increased bone resorption in males. Additionally, haemophilia is predominantly a male disease, so the findings in male mouse models are of greater clinical importance.

3.4 | Weight-bearing exercises

The WFH guidelines encourage PWH of all ages to engage in weight-bearing activities and sport to promote and maintain BMD.[2] As joint

TABLE 2 Summary of ESSA exercise recommendations for osteoporosis prevention and treatment

Type of exercise	Recommended frequency and repetitions	Example exercises
High-intensity progressive resistance training	Twice per week, 2–3 sets of eight repetitions	Squats, weighted deadlifts, weighted lunges, reverse chest fly, back extensions
Moderate-high impact loading activities	Four to seven times per week, 50 repetitions spread over 3–5 sets	Skipping, bench stepping, vertical and multidirectional jumping, bounding
Balance training	Four times per week, around 30 min	Tai Chi, walking backwards, walking sideways, single leg stance, pivot turns, stepping over obstacles

Modified from Beck et al., 2017.[68]

disease may limit participation, PWH are encouraged to see a physical therapist prior to commencing any activity for guidance on appropriateness, protective gear, bracing of target joints and prophylaxis required.[2] Supervised physical therapy is recommended for PWH with musculoskeletal injuries or disease.[2] Australian guidelines mirror this exercise advice.[29] British guidelines recommend regular exercise to improve musculoskeletal function.[28]

Weight-bearing activity is particularly important in childhood and adolescence as it is hypothesised that reaching a 10% higher peak bone mass could delay osteoporosis onset and reduce lifetime fracture risk by 50%.[66] The effect of weight-bearing exercise on BMD in adulthood is much smaller at around 1–3%,[67] as it mainly acts by slowing the age-related decline in BMD.[7] Exercise and Sports Science Australia (ESSA) has an exercise programme for osteoporosis prevention and treatment that includes resistance training and impact loading activities (Table 2),[68] which may be beneficial for bone health in PWH. However, PWH with severe disease have reduced functional capacity due to arthropathy.[69] Therefore, it is important to assess whether PWH can participate in resistance training safely.

A randomised control trial (RCT) in PWH (n = 16, mean age 41.8 years, mean weight 64.3 kg for the intervention group) trialled an 8-week home exercise programme focused on improving knee function, a common site of haemophilic arthropathy.[70] Exercises included strengthening of knee extension, stretching and balance and significant improvements were found in knee extension strength, range of knee extension and ankle dorsiflexion, the modified-Functional Reach Test and 10 m gait time.[70] It is unclear whether the exercises in this study are of sufficient intensity, impact and resistance to alter BMD. However, the functional improvements may enable PWH to participate in more appropriate resistance training exercises. Another RCT in 32 patients with moderate-severe haemophilia involved a 6-month strength, endurance, mobility and coordination programme.[71] Exercises (i.e. leg press and cable pull exercises) utilised exercise machines for 90 min twice per week and were of increasing intensity over the study period.[71] The RCT found a significant improvement in strength performance of 8 muscle groups, balance and gait speed.[71] Importantly, both RCTs established that there was no increased bleeding risk with this type of training.[70,71] As PWH can participate in weight-bearing activities safely, future studies focusing on the effectiveness of resistance exercises for BMD improvement are warranted.

3.5 | Falls prevention

Falls prevention is not specifically addressed in any haemophilia guideline but inferences can be made from the musculoskeletal advice. The Australian and WFH guidelines recommend that PWH have a team of musculoskeletal specialists, who should conduct a musculoskeletal assessment annually in adults and 6-monthly in children.[2,29] Physiotherapy and rehabilitation are highly recommended for musculoskeletal complications, with emphasis on exercise for muscle strengthening and balance, and early physiotherapy to avoid prolonged immobilisation.[2,29] British guidelines infer similar falls advice.[28]

Falls are a major contributor to fractures in PWH and so necessitate haemophilia guidelines to include a section on fall prevention. Studies show that 53–81% of fractures in PWH are due to a fall from a standing height or less.[8,38,39] The annual falls prevalence is 32–50% in PWH (mean age 54.2 years[72] and 39.4 years,[73] respectively) with 30–42% of PWH having subsequent falls in this timeframe.[72,73] In the general population the annual falls prevalence is 28–35% in adults aged over 65 years[74]; although the annual falls prevalence in PWH is similar to this, falls occur at a substantially younger age. Factors associated with falls in PWH include poor balance, mobility impairment, weakness, poorer orthopaedic status, impaired gait, urinary incontinence, uneven terrain and apartment living.[72,73] PWH should have a falls screening test at their reviews and if deemed to be at risk, they should undergo a full falls assessment and be engaged in a balance programme, such as the programme suggested by ESSA.[68] Screening questions should identify patients with gait or balance problems or who have had falls,[30] while the timed up and go test has been recommended as a functional screening test for PWH.[5] Exercises including Tai Chi, dual task training and back extension stretches to oppose kyphosis have been shown to reduce falls.[68] Additionally, two RCTs report that training in PWH can improve balance, measured by improvements in one-leg stand and modified-Functional Reach Test.[70,71] Further research is needed to assess the efficacy of falls prevention strategies in PWH.

4 | CONCLUSION

Early diagnosis and treatment of osteoporosis in PWH is important as fractures lead to significant morbidity and mortality. Time for

fracture recovery is significant in PWH as prolonged periods of immobility lead to muscular deconditioning, poorer bone health and increased falls and fracture risk. It is yet unknown whether reduced thrombin generation, factor VII, factor IX and/or IIA generation deficiency in haemophilia itself, are contributing to low BMD. There is an overall lack of research on musculoskeletal health in PWH. As such, World, British and Australian haemophilia guidelines lack clear recommendations for osteoporosis screening, treatment and management in PWH. Determining the effectiveness of screening programmes and anti-osteoporosis treatment in adults and children with haemophilia will improve the management of musculoskeletal health in PWH.

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AUTHOR CONTRIBUTIONS

MJP and AZ contributed to study design and performed the research; all authors contributed to the development and review of the manuscript.

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