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REVIEW ARTICLE

WILEY Haemophilia

Prevalence and impact of obesity in people with haemophilia: Review of literature and expert discussion around implementing weight management guidelines

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Obesity affects more than 35% of Americans, increasing the risk of more than 200 comorbid conditions, impaired quality of life and premature mortality. This review aimed to summarize literature published over the past 15 years regarding the prevalence and impact of obesity in people with haemophilia (PWH) and to discuss implementing general guidelines for weight management in the context of the haemophilia comprehensive care team. Although few studies have assessed the effects of obesity on haemophilia-specific outcomes, existing evidence indicates an important impact of weight status on lower extremity joint range of motion and functional disability, with potentially important effects on overall quality of life. Data regarding bleeding tendency in PWH with coexisting obesity are largely inconclusive; however, some individuals may experience reduced joint bleeds following moderate weight loss. Additionally, conventional weight-based dosing of factor replacement therapy leads to increased treatment costs for PWH with obesity or overweight, suggesting pharmacoeconomic benefits of weight loss. Evidence-based recommendations for weight loss include behavioural strategies to reduce caloric intake and increase physical activity, pharmacotherapy and surgical therapy in appropriate patients. Unique considerations in PWH include bleed-related risks with physical activity; thus, healthcare professionals should advise patients on types and intensities of, and approaches to, physical activity, how to adjust treatment to accommodate exercise and how to manage potential activity-related bleeding. Increasing awareness of these issues may improve identification of PWH with coexisting obesity and referral to appropriate specialists, with potentially wide-ranging benefits in overall health and well-being.

KEYWORDS
comorbidities, haemophilia, health behaviour changer, obesity, overweight, weight loss

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1 | INTRODUCTION

Obesity is associated with more than 200 comorbid conditions,[1] impaired quality of life[2] and premature mortality.[3] The prevalence of obesity has tripled since the 1970s in the United States and is increasing at an even greater pace in much of the world.[4,5] As such, preventing and treating obesity is a critical target for combating preventable disease and has become a focus of many public health initiatives in the United States and around the world.[6] Published clinical practice guidelines provide detailed assessments of the impact of obesity in the general population along with aims and strategies for weight loss interventions.[7,8] However, few studies have focused on the implications of these findings for specific patient populations, including for people with haemophilia (PWH).

Haemophilia is a chronic disease characterized by excessive bleeding, often into joints, which over time may result in progressive arthropathy, functional impairment and chronic joint pain.[9] This constellation of symptoms suggests a potentially aggravating effect of obesity on joint health, as well as barriers towards engagement in physical activity, which may limit an individual's ability to maintain a healthy weight. Although a comprehensive understanding of the impact of obesity on haemophilia has yet to be established, emerging evidence from the general population supports consideration of obesity as an important health concern. In this report, we review the literature assessing the impact of obesity on haemophilia-specific outcomes and discuss evidence-based weight management recommendations. We aim to provide a greater understanding of the unique benefits and challenges of weight loss among PWH with coexisting obesity or overweight.

1.1 | The obesity epidemic

Within the overall population, the broad impact of obesity on health and well-being has been thoroughly investigated and offers insight into the risk and impact of obesity among PWH. Overweight and obesity in adults are defined as having a body mass index (BMI) of 25-29.9 kg/m^2 and ≥30 kg/m^2, respectively. In the United States, obesity in adults has risen threefold since the 1970s.[4] More than 35% of US adults have obesity, and an additional 34% of adults are characterized as overweight.[10] Particularly alarming is the dramatic increase in the prevalence of severe obesity (BMI ≥40 kg/m^2), which has increased by more than 600% since the 1980s.[10-12] Prevalence rates are significantly higher among Hispanic adults and non-Hispanic black adults (47.8%), with a strong gender interaction. Within the paediatric population, ideal BMI varies with age, and therefore, weight status is usually determined through comparisons to age- and gender-specific BMI reference standards (i.e BMI percentile or percentage above the 95th percentile).[13] Approximately 31.6% of US children (aged 2-19 years) meet criteria for overweight (BMI ≥85th percentile of Centers for Disease Control and Prevention [CDC] gender-specific BMI-for-age growth charts from 2000[14,15]), including 16.9% categorized as having obesity (BMI ≥95th percentile).[10]

The medical burden of obesity is profound, accounting for an estimated $3559 in annual per-patient medical expenditures in the general population.[7] A large number of comorbidities associated with excessive weight contribute to this burden. In particular, obesity is an independent risk factor for coronary heart disease, type 2 diabetes, stroke, hypertension, dyslipidaemia, insulin resistance and non-alcoholic fatty liver disease.[16-18] Obesity is also associated with increased prevalence of numerous cancers, through mechanisms thought to primarily involve hyperinsulinaemia, activation of proinflammatory signalling pathways and alterations in endogenous hormone metabolism.[19] Obesity additionally contributes to disorders of excessive fat mass, such as osteoarthritis and obstructive sleep apnoea, and mental health disorders such as depression, with significant effects on medical care utilization and overall quality of life.[7]

2 | LITERATURE REVIEW

2.1 | Study selection

This review aimed to summarize literature regarding the prevalence and impact of obesity specifically in PWH. Published studies were identified through a search of literature published within the last 15 years using the electronic databases Scopus and InsightMeme. Search terms consisted of "obese OR obesity OR overweight OR BMI OR body mass index OR weight" AND "hemophilia OR haemophilia OR hemophiliac OR haemophiliac." References cited within these records were also manually reviewed for additional records of interest. Records were excluded if they contained no original data, no relevant data, duplicate study data or if they presented data regarding the prevalence of cardiovascular disease without including any control (non-haemophilia) population with which to compare prevalence estimates. Records were categorized by topic, resulting in five distinct categories: obesity prevalence, musculoskeletal health, bleeding tendency, cardiovascular disease and dosing considerations.

A total of 92 records were identified and assessed for inclusion in the analysis by a single reviewer (Figure 1). Of these, 55 were excluded and 37 remained in the final analysis. A comprehensive list of these publications and summary of relevant data are presented in Supplementary Table S1.

2.2 | Obesity prevalence

In PWH, the prevalence of overweight (adults, 19%-59%; children, 15%-21%) and obesity (adults, 18%-36%; children, 17%-22%) is similar to that of the general US population.[20-31] Existing evidence suggests minimal correlation between haemophilia severity and risk of obesity, although few studies have evaluated this relationship. A retrospective review of 132 patient charts from the Mississippi Hemophilia Treatment Center (HTC) found no significant differences in rates of overweight or obesity between those with severe vs mild or moderate haemophilia.[22] Furthermore, conflicting reports were obtained from a Dutch postal survey that found severe haemophilia to be associated with lower rates of overweight[32] and a Canadian paediatric chart review that found severe haemophilia to be associated with higher rates of obesity.[33] Existing evidence also suggests a

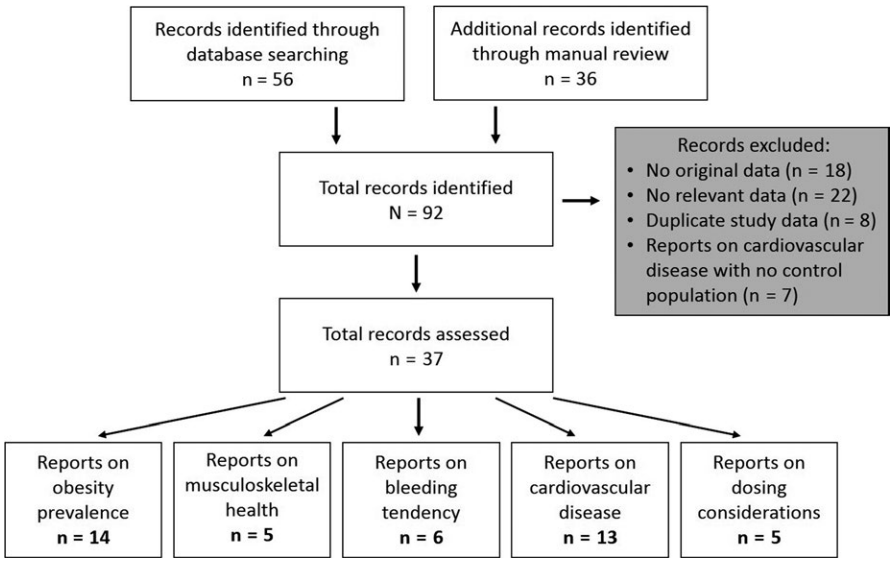

FIGURE 1 Study selection

minimal effect of joint symptoms on risk of obesity, as participants in the Pain, Functional Impairment and Quality of Life (P-FiQ) study, who were selected for the presence of joint pain or bleeding, showed no apparent increase in rates of overweight (36%) or obesity (29%), compared with the general population.[28] The Universal Data Collection (UDC) programme, a collection of surveillance data provided by US HTCs in collaboration with the CDC, identified similar prevalences of overweight or obesity among adults (age 20+ years) in the haemophilia and general populations (overweight: 34.5% vs 32.6%; obese: 23.5% vs 22.3%).[31]

Of note, potential confounding factors in assessing the effects of haemophilia on weight status are the presence of muscle atrophy that may accompany joint disease and comorbid human immunodeficiency virus infection, each of which may decrease BMI and therefore lead to an underestimation of adiposity.[23,34] Future clinical or research-based assessments of obesity among PWH may therefore benefit from a consideration of body composition in the context of BMI measurements.

2.3 | Musculoskeletal health

Many studies regarding haemophilia and obesity have focused on complications of the musculoskeletal system, as joint pain and functional disability are critical complications of haemophilia and intuitively linked to obesity through potentially convergent effects on joint damage and range of motion (ROM). Haemophilic joint disease is a consequence of recurrent joint bleeding, which over time causes intra-articular blood-induced damage of the cartilage and synovium, in processes resembling both osteoarthritis and rheumatoid (inflammatory) arthritis.[9] Obesity and adiposity are also strongly associated with osteoarthritis and musculoskeletal pain, through pathways triggered primarily by mechanical stress and subsequent cartilage degradation.[35] Systemic adipose factors have also been implicated in obesity-induced osteoarthritis, particularly regarding non-weight-bearing joints such as the hands and elbows, and may mediate a distinct pathway contributing to joint disease.[36]

Much of the evidence regarding the effects of obesity on haemophilic arthropathy comes from analyses of UDC data. Data collected between 1998 and 2002 referencing 4965 young males (aged 2-19 years) identified a statistically significant relationship between BMI and limitations in overall joint ROM at each level of haemophilia severity (mild, moderate and severe).[37] Additionally, a follow-up study was designed to track longitudinal outcomes of childhood obesity (over a 10-year period) using UDC data from 6347 males with haemophilia aged 2 to 20 years.[26] Individuals with obesity at baseline exhibited a lower initial ROM score, as well as a faster rate of mobility loss in the lower limbs, suggesting an accelerating effect of obesity on the loss of ROM in the weight-bearing joints. An additional study investigating ROM limitations assessed numbers of target joints and joints with reduced mobility among children and young adults with haemophilia from a single US centre.[38] Results of this analysis found individuals with BMI at or above the 85th percentile to exhibit significantly greater odds (3.4, 95% CI, 1.1-10.7) of having at least one target joint or joint with ROM outside the range of normal, consistent with important effects of obesity on haemophilic joint damage.

In addition to these reports of mobility loss, functional correlates of physical disability were investigated in a study of 6419 young males with haemophilia (aged ≤18 years) using UDC data collected between 1998 and 2008.[24] As determined by multivariate analysis, individuals with obesity reported significantly greater levels of disability, as measured using three independent indicators (i.e having lost more than 11 days of work or school during the past year; requiring use of a cane, crutches or a walker; and requiring use of a wheelchair). Lower limb functional limitations were further supported by an analysis of functional ability using the Hemophilia Activities List (HAL) patient-reported outcome instrument in a study from a single institution in the Netherlands.[39] Compared with adults without obesity, those with obesity reported significantly lower HAL scores on all domains related to function of the lower extremities (basic lower extremity function, complex lower extremity function, lying/sitting/kneeling/standing and leg functions).

2.4 | Bleeding tendency

Existing evidence has not demonstrated a consistent correlation between weight status and bleeding risk in PWH, although few studies have examined this relationship. One small (n=30) study of adults with haemophilia A demonstrated a significantly higher number of bleeding episodes requiring factor VIII (FVIII) treatment experienced by individuals with obesity, as compared with those without obesity, during a 2-year study period[39]; however, three cross-sectional analyses of individuals with haemophilia found no significant differences in bleeding rates between populations with and without obesity.[38,40,41] Overall, potential variability in levels of physical activity, intrinsic bleeding tendency and treatment characteristics (only Recht et al. incorporated a fixed treatment regimen[40]), as well as relatively small sample sizes, limit our ability to form strong conclusions based on these data.

Limited data exist on the longitudinal impact of obesity and changes of weight, although potentially important relationships between weight and frequency of bleeding in the ankles (r^2=.418), elbows (r^2=.927) and knees (r^2=.899) were observed within a case report of a single individual with obesity and severe haemophilia who underwent an approximately 4-month period of weight reduction.[42] Similarly, a separate case report examined rates of bleeding before and after substantial weight loss in a man with both severe obesity and severe haemophilia who had undergone bariatric surgery.[43] Although his overall rate of bleeding did not change, the authors report that he experienced notably fewer joint bleeds, and an increase in soft tissue and muscle bleeds was largely attributed to increased physical activity.

2.5 | Cardiovascular disease and risk factors

Because of the important role of obesity as a risk factor for coronary heart disease, assessment of the impact of obesity in any patient population is likely to include a consideration of cardiovascular health. Haemophilia has traditionally been viewed as offering protection from thrombosis, due to the induction of a hypocoagulable state, and has been associated with a significantly reduced risk for venous thromboembolism. However, the relationship between haemophilia and cardiovascular risk is not as well understood.[44]

Numerous assessments of cardiovascular risk among PWH compared with the general population have been performed, although no consensus has been reached as to whether a protective effect of haemophilia is conferred. Our search identified 13 records that reported on cardiovascular risk among PWH compared with the general population. Of those that assessed the relative prevalence of cardiovascular disease or mortality, one supported a protective effect of haemophilia, three indicated a potential negative effect of haemophilia, and two found no substantial effect of haemophilia.[45-50] However, methodological concerns and mostly small sample sizes limit interpretation of these results and suggest the need for a large prospective study.

Many studies have also investigated the effects of haemophilia on specific risk factors for cardiovascular disease, as assessment of individual factors may clarify the understanding of the relationship between haemophilia and overall cardiovascular risk. In general, assessments of risk factors including diabetes, dyslipidaemia and atherosclerosis reflect many of the same methodological limitations and inconclusive or contradictory results that have been reported in the context of cardiovascular disease.[45-58] However, hypertension appears to be a notable exception, as existing evidence consistently supports an increased prevalence among PWH.[45,46,49,54-57] Although data regarding a pathogenic mechanism of hypertension in the context of haemophilia are lacking, recent studies among large cohorts have reported an increase in prevalence compared with the general population, ranging from 23% to 61%. Of note, hypertension may be particularly worrisome in the context of haemophilia due to a strong correlation with intracranial haemorrhage, a potentially lethal bleeding event.

2.6 | Pharmacokinetics and dosing considerations

Replacement of deficient coagulation factors is the cornerstone of treatment for managing and preventing bleeding episodes in people with moderate or severe haemophilia and as such represents a critical determinant of haemophilia-specific outcomes. The traditional goal of factor replacement based on pharmacokinetics of available products has been treatment three times weekly with FVIII (haemophilia A) or twice weekly with factor IX (FIX; haemophilia B) to maintain trough FVIII/FIX activity of at least 1%. However, therapeutic targets for prophylaxis are commonly personalized to accommodate clinical response (breakthrough bleeding), individual patient pharmacokinetics and joint status (including the presence of target joints). Particularly when infused on a routine basis to prevent bleeding, underuse of factor replacement therapy may have consequences on long-term outcomes (e.g joint pain and function). However, higher use may significantly increase treatment costs and should be critically evaluated to ensure appropriate pharmacoeconomic tenability.

Among PWH with coexisting obesity, accumulating evidence demonstrates a significantly increased in vivo recovery of factor replacement products.[59,60] Because fatty tissue contains less blood than lean body mass, dosing based on body weight likely overestimates total blood volume, leading to higher recovery and a potential for greater trough activity levels compared with equivalent per kilogram dosing in individuals of normal weight. However, the only pivotal registration study in which clinical outcomes were assessed across weight categories demonstrated similar annualized bleeding rates in obese and non-obese individuals when dosed by body weight.[40] In contrast, ideal-weight-based dosing of FVIII has been reported for routine prophylactic infusions as well as continuous infusion during surgery among small populations of people with haemophilia A and is associated with similar pharmacokinetics (peak level and half-life) compared with standard dosing regimens.[61,62] In the absence of any studies in which patients were randomized to different trough levels, the issue of the most appropriate minimal factor activity target for prophylaxis remains unclear. Furthermore, the presence of lower extremity joint problems among overweight individuals with haemophilia might suggest that this population could benefit from slightly higher factor activity.

Given that haemophilia treatment is based on body weight, it would follow that moderate weight loss could result in substantial

TABLE 1 Theoretical FVIII savings associated with weight loss

	BMI, kg/m^2	Weight, kg	Weight, lb	Annual FVIII usage, IU	Annual FVIII savings with 5% weight loss, IU	Annual FVIII savings with 10% weight loss, IU
Normal weight	21.7	67.2	148.2	350 493	—	—
Overweight	25	77.4	170.7	403 794	20 190	40 379
Obesity	30	92.9	204.9	484 553	24 228	48 455
Severe obesity	40	123.9	273.2	646 071	32 304	64 607

BMI, body mass index; FVIII, factor VIII; IU, International Unit.
Assumptions: height, 1.76 m; dosing regimen, 100 IU/kg/wk.

pharmacoeconomic benefits. As a hypothetical example, a male with a BMI of 30 kg/m^2, of average height (1.76 m [69 in.]) and weighing 93 kg (205 lb), using a standard FVIII dosing regimen for prophylaxis (100 IU/kg/wk across three infusions), would be expected to use 484 553 IU of FVIII per year (Table 1). Achieving a 5% to 10% reduction in initial weight would potentially result in a direct and parallel reduction in factor cost that could more than offset the costs of any weight loss interventions. Even if the individual were to gradually gain back weight, the net savings in the short-term would still be significant.

An additional mechanism through which obesity may influence treatment outcomes is through potential effects on individuals' ability to self-infuse clotting factor products or bypassing agents. Analysis of a large number of PWH (N=10 814) within the UDC database indicated significantly lower rates of self-infused and home-infused treatments among individuals with obesity vs those of normal weight, which may be attributed to challenges in visualizing veins due to excessive adiposity.[27] Because an inability to infuse in the home setting may limit individuals' access to timely treatment for acute bleeding episodes or adherence to a routine dosing regimen, weight loss may be an important means to improve treatment-related outcomes among some PWH with coexisting obesity.

3 | APPLICATION OF GENERAL GUIDELINES FOR WEIGHT MANAGEMENT

Considering the numerous potential causes and complications of obesity, optimal approaches to weight loss incorporate nuanced clinical decision-making and individualized care.[7,8] While no specific guidelines exist for weight management in PWH, existing guidelines for children and adults do not exclude application to patients with underlying disorders. Specific treatment approaches (e.g appropriate physical activities/exercise, bariatric surgery) may need to be considered differently in PWH and involve multistakeholder HTC input in applying general weight management guidelines.

Comprehensive lifestyle modification is the basis of interventions to prevent weight gain or promote weight loss, and broadly incorporates efforts to decrease caloric intake, increase physical activity

TABLE 2 Guidelines for weight management

Adults[8]		Children and adolescents[69,70]	
Weight status	**Recommendation**	**Weight status**	**Recommendation**
BMI 25-29.9 kg/m^2 without indicators of cardiovascular risk	Avoid additional weight gain	BMI 85th-94th percentile with health risks or BMI ≥95th percentile	Prevention Plus: diet, exercise and television recommendations implemented by a trained primary care physician or allied healthcare provider
BMI 25-29.9 kg/m^2 with indicators of cardiovascular risk	Comprehensive lifestyle intervention	BMI 85th-94th percentile with health risks or BMI ≥95th percentile, after trial of Prevention Plus; or BMI >99th percentile if patient/family are motivated and patient is at least 6 years of age	Structured Weight Management: structured and reinforced diet, exercise and television recommendations implemented by a highly trained primary care physician or allied healthcare provider
BMI 30-39.9 kg/m^2 or BMI ≥27 kg/m^2 with indicators of cardiovascular risk	Comprehensive lifestyle intervention alone or with adjunctive pharmacotherapy	BMI ≥95th percentile, after trial of Structured Weight Management; or BMI >99th percentile if patient/family are motivated and patient is at least 6 years of age	Comprehensive Multidisciplinary Intervention: implementation of a negative energy balance achieved through structured diet, exercise and behavioural modification and frequent office visits, ideally with a multidisciplinary obesity care team
BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 with indicators of cardiovascular risk	Comprehensive lifestyle intervention, with referral to a bariatric surgeon offered for evaluation as adjunctive therapy	BMI >95th percentile and age 12-18 years or BMI >99th percentile and age 6-11 years, after trial of Comprehensive Multidisciplinary Intervention and if appropriate	Tertiary Care Intervention: referral to a paediatric tertiary weight management centre with access to a multidisciplinary team with expertise in childhood obesity, operating under a designed protocol

BMI, body mass index.

and establish behavioural changes that promote adherence to these changes in diet and exercise.[63] More intensive approaches, including pharmacotherapy and bariatric surgery, are recommended for individuals with obesity-related comorbid conditions and/or higher weight status (Table 2), especially for those with severe obesity and in situations in which behavioural therapy alone has been insufficient to achieve meaningful weight loss. Obesity medicine specialists may be helpful in determining whether pharmacotherapy or bariatric surgery (assuming a careful consideration of surgical risks) may be warranted; of note, for PWH, appropriate haemostatic coverage during surgery should be administered in the perioperative setting under the direction of the HTC.

A reduction in caloric intake should be the main component of any weight loss intervention, and may be achieved by targeting a specific caloric target (1200-1500 kilocalories/day for women and 1500-1800 kilocalories/day for men) or energy deficit (500 or 750 kilocalories/day) or by restricting consumption of particular foods or food groups.[7,8] Little evidence suggests that calorie-neutral changes in the macronutrient composition of meals have any direct impact on weight loss. However, consideration of macronutrient consumption may be useful in optimizing adherence or managing specific risks, such as hypertension or cardiovascular disease.[64] Tailoring the prescription for a reduced calorie diet to accommodate patients' personal preferences and barriers, such as geographic, financial, cultural or familial circumstances, may also be critical in establishing an effective weight loss programme.

Physical activity is an additional important component of weight loss interventions, particularly during the process of maintaining lost weight. Evidence-based recommendations support individualized exercise regimens that include aerobic activity (working up to 150 minutes or more of moderate exercise per week, distributed across three to five daily sessions), resistance training (two to three times per week) and active leisure activity.[7] In the context of haemophilia, however, a careful consideration of the individual's risk of bleeding (both real and perceived) and level of pain and functional impairment is critical in designing a safe and effective exercise regimen. For example, important steps to facilitate regular activity may include selecting low-impact aerobic activities such as swimming, walking or cardiovascular training using an elliptical machine or stationary bike, reducing the intensity of resistance exercises, incorporating a stretching routine and recognizing and managing the risk of activity-related pain or bleeding.[65-68] Advising PWH on which types and intensities of activities to engage in, how to adjust their treatment regimens to accommodate exercise and how to manage potential activity-related bleeding are therefore important responsibilities of the haemophilia care team. A general guideline for determining which types of activities are appropriate for PWH at different ages has been provided by the National Hemophilia Foundation[65] and may be useful for healthcare professionals (HCPs), patients and their families; however, any exercise regimen should also broadly consider personal preferences, history of activity-related bleeding and specific functional limitations.

The third component of comprehensive lifestyle intervention is behavioural therapy, which may include personalized interventions such as weight and behavioural self-monitoring, goal-setting, education, psychological counselling, stress reduction and mobilization of social support.[7,8] These approaches should preferably involve high-frequency (i.e at least 14 sessions over 6 months) face-to-face individual or group sessions led by a trained interventionist, as well as personalized feedback. In the context of overweight children or adolescents, assessing behaviours of parents and caregivers that may contribute to weight gain and achieving commitment of family members in weight loss efforts may be critical steps.[69,70] Of note, the chronic disease model for comprehensive care of PWH aligns well with the general approach towards behavioural intervention, and emerging use of telemedicine in comprehensive management for PWH living far from an HTC[71] may be adapted to support behavioural intervention. Because PWH are typically accustomed to multidisciplinary and patient-centric efforts to improve outcomes, targeting incremental improvements that accrue over time and regular communication with HCPs, this patient population may be well suited for engagement with weight management professionals. Additionally, psychosocial support provided by the HTC team (e.g building from long-term relationships and frequent personal contact) may help to improve motivation and adherence to weight loss plans. Setting realistic and meaningful goals and expectations regarding weight loss intervention is a central aspect of behavioural therapy. Although personal weight loss goals will be influenced by the presence of obesity-related comorbidities and the individual's readiness to make lifestyle changes, sustained loss of as little as 3%-5% of body weight may confer significant metabolic benefits, and loss of 5%-10% of body weight within 6 months is recommended as an initial goal.[7,8]

In the context of comprehensive haemophilia care, routine monitoring of weight and BMI status and establishing standardized protocols for patient referral to nutritionists or other weight management specialists may be important initial steps in identifying and treating weight issues. Because few HTCs have written protocols or guidelines to address weight issues,[72] developing a standardized approach towards collaboration with weight management experts may be an important unmet need. Individuals referred to weight management specialists should be advised that obesity is a chronic condition, and therefore, continued weight maintenance interventions are necessary to prevent weight regain.

4 | CONCLUSIONS

The study of the broad impact of obesity on haemophilia-specific outcomes is currently in its infancy. However, existing evidence in PWH suggests high obesity prevalence and important effects on joint function, physical disability and venous access for the administration of factor replacement products. Furthermore, evidence from the general population suggests wide-ranging benefits of weight loss. Given weight-based dosing of haemophilia treatment, weight reduction has potential short-term and long-term cost savings that likely exceed costs of weight management interventions.

TABLE 3 Unmet research and HTC needs

Research needs
• Large-scale assessments of the impact of haemophilia characteristics (e.g disease severity, joint damage) on risk of obesity • Longitudinal assessments of bleeding tendency and musculoskeletal function experienced by PWH during periods of weight gain or weight loss, including identification of weight loss thresholds for improvement • Large prospective cohort studies of relative risk of cardiovascular disease in PWH • Efforts to understand perspectives of PWH with coexisting overweight or obesity regarding barriers towards and opportunities for weight loss • Investigation of pharmacokinetics in PWH with coexisting overweight or obesity to better identify ways to optimize and adjust dosing
HTC needs
• Standardized protocols for assessing weight status (including identification of weight issues in children and adolescents) and referring overweight individuals to appropriate specialists • Awareness of the benefits of weight loss (medical and pharmacoeconomic) among PWH with coexisting obesity

HTC, haemophilia treatment centre; PWH, people with haemophilia.

Future directions of study should include a proof of concept regarding multicomponent therapies in PWH with comorbid obesity to identify weight loss thresholds for improvements in musculoskeletal function and bleeding tendency, in addition to confirming potential pharmacoeconomic savings (Table 3). Subsequently, large-scale assessments could be performed within existing patient cohort studies to evaluate the impact of weight gain and weight loss on bleeding tendency, which will be necessary to accurately assess weight-related outcomes. A greater understanding of clinical outcomes associated with weight management approaches and patient and HCP perceptions regarding weight issues may facilitate the establishment of evidence-based weight management guidelines specific to the haemophilia experience. In the context of our current understanding of weight issues in PWH, HCPs involved in the comprehensive care of PWH should be aware of how to accurately monitor weight status and collaborate with weight management specialists to implement weight loss interventions for their patients with overweight or obesity.

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REFERENCES

1. Yuen M, Earle R, Kadambi N, et al. A systematic review and evaluation of current evidence reveals 236 obesity-associated disorders. *The Obesity Society*. New Orleans, LA: T-P-3166, 2016.
2. Kushner RF, Foster GD. Obesity and quality of life. *Nutrition*. 2000;16:947–952.
3. Whitlock EP, O'Connor EA, Williams SB, Beil TL, Lutz KW. Effectiveness of weight management interventions in children: a targeted systematic review for the USPSTF. *Pediatrics*. 2010;125:e396–e418.
4. Fryar CD, Carroll MD, Ogden CL. Prevalence of overweight, obesity, and extreme obesity among adults: United States, 1960–1962 through 2011–2012. *National Center for Health Statistics Health E-Stats*: https://www.cdc.gov/nchs/data/hestat/obesity_adult_11_12/obesity_adult_11_12.htm. Accessed June 1, 2017.
5. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384:766–781.
6. Gortmaker SL, Swinburn BA, Levy D, et al. Changing the future of obesity: science, policy, and action. *Lancet*. 2011;378:838–847.
7. Garvey WT, Mechanick JI, Brett EM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity. *Endocr Pract*. 2016;22(Suppl 3):1–203.
8. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol*. 2014;63:2985–3023.
9. Roosendaal G, Lafeber FP. Pathogenesis of haemophilic arthropathy. *Haemophilia*. 2006;12(Suppl 3):117–121.
10. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA*. 2014;311:806–814.
11. Kuczmarski RJ, Carroll MD, Flegal KM, Troiano RP. Varying body mass index cutoff points to describe overweight prevalence among US adults: NHANES III (1988 to 1994). *Obes Res*. 1997;5:542–548.
12. Sturm R. Increases in morbid obesity in the USA: 2000-2005. *Public Health*. 2007;121:492–496.
13. Skinner AC, Perrin EM, Skelton JA. Prevalence of obesity and severe obesity in US children, 1999-2014. *Obesity (Silver Spring)*. 2016;24:1116–1123.
14. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC growth charts for the United States: methods and development. *Vital Health Stat 11*. 2002:1–190.

15. Ogden CL, Flegal KM. Changes in terminology for childhood overweight and obesity. *Natl Health Stat Report*. 2010;1–5.
16. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol*. 2009;53:1925–1932.
17. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Arterioscler Thromb Vasc Biol*. 2006;26:968–976.
18. Abenavoli L, Milic N, Di Renzo L, Preveden T, Medic-Stojanoska M, De Lorenzo A. Metabolic aspects of adult patients with nonalcoholic fatty liver disease. *World J Gastroenterol*. 2016;22:7006–7016.
19. Klil-Drori AJ, Azoulay L, Pollak MN. Cancer, obesity, diabetes, and antidiabetic drugs: is the fog clearing? *Nat Rev Clin Oncol*. 2016;14:85–99.
20. Curtis R, Baker J, Riske B, et al. Young adults with hemophilia in the US: demographics, comorbidities, and health status. *Am J Hematol*. 2015;90(Suppl 2):S11–S16.
21. Lim MY, Pruthi RK. Cardiovascular disease risk factors: prevalence and management in adult hemophilia patients. *Blood Coagul Fibrinolysis*. 2011;22:402–406.
22. Majumdar S, Morris A, Gordon C, et al. Alarmingly high prevalence of obesity in haemophilia in the state of Mississippi. *Haemophilia*. 2010;16:455–459.
23. McNamara M, Antun A, Kempton CL. The role of disease severity in influencing body mass index in people with haemophilia: a single-institutional cross-sectional study. *Haemophilia*. 2014;20:190–195.
24. Monahan PE, Baker JR, Riske B, Soucie JM. Physical functioning in boys with hemophilia in the US. *Am J Prev Med*. 2011;41:S360–S368.
25. Sood SL, Cheng D, Ragni MV, et al. A cross-sectional analysis of cardiovascular disease in the hemophilia population. *Blood*. 2015;126:761.
26. Soucie JM, Wang C, Siddiqi A, et al. The longitudinal effect of body adiposity on joint mobility in young males with haemophilia A. *Haemophilia*. 2011;17:196–203.
27. Ullman M, Zhang QC, Brown D, Grant A, Soucie JM. Hemophilia Treatment Center Network I. Association of overweight and obesity with the use of self and home-based infusion therapy among haemophilic men. *Haemophilia*. 2014;20:340–348.
28. Witkop M, Neff A, Buckner TW, et al. Self-reported prevalence, description, and management of pain in adult people with hemophilia from the pain, functional impairment, and quality of life (P-FiQ) study. *Am J Hematol*. 2016;91:E363–E430.
29. Centers for Disease Control and Prevention Universal Data Collection. Summary report of UDC activity national: risk factors by age (hemophilia). 2011.
30. Ullman M, Kuebler E, Du Treil S, Moynihan K. Increased body mass index in persons with hemophilia. *Am J Hematol*. 2006;12:16 FP 460.
31. Centers for Disease Control and Prevention. Report on the Universal Data Collection Program. Atlanta, GA: Centers for Disease Control and Prevention; July 2005. https://www.cdc.gov/ncbddd/blooddisorders/udc/documents/report-udcprogram_may-1998-december-2004_july-2005.pdf. Accessed June 1, 2017.
32. Hofstede FG, Fijnvandraat K, Plug I, Kamphuisen PW, Rosendaal FR, Peters M. Obesity: a new disaster for haemophilic patients? A nationwide survey. *Haemophilia*. 2008;14:1035–1038.
33. Revel-Vilk S, Komvilaisak P, Blanchette V, et al. The changing face of hepatitis in boys with haemophilia associated with increased prevalence of obesity. *Haemophilia*. 2011;17:689–694.
34. Fransen van de Putte DE, Fischer K, Roosendaal G, Hoepelman AI, Mauser-Bunschoten EP. Morbidity and mortality in ageing HIV-infected haemophilia patients. *Haemophilia*. 2013;19:141–149.
35. Pottie P, Presle N, Terlain B, Netter P, Mainard D, Berenbaum F. Obesity and osteoarthritis: more complex than predicted!. *Ann Rheum Dis*. 2006;65:1403–1405.
36. Pan F, Laslett L, Blizzard L, et al. Associations between fat mass and multi-site pain: a 5-year longitudinal study. *Arthritis Care Res (Hoboken)*. 2017;69:509–516.
37. Soucie JM, Cianfrini C, Janco RL, et al. Joint range-of-motion limitations among young males with hemophilia: prevalence and risk factors. *Blood*. 2004;103:2467–2473.
38. Carpenter SL, Chrisco M, Johnson E. The effect of overweight and obesity on joint damage in patients with moderate or severe hemophilia. *Blood*. 2006;108:4064.
39. Biere-Rafi S, Haak BW, Peters M, Gerdes VE, Buller HR, Kamphuisen PW. The impairment in daily life of obese haemophiliacs. *Haemophilia*. 2011;17:204–208.
40. Recht M, Lentz SR, Zupancic-Salek S, Matytsina I, Landorph A, Saugstrup T. Factor VIII dosing and preventive efficacy in obese patients with hemophilia (BMI ≥30 kg/m^2) – a post-hoc sub-analysis of the guardian™ trials. *Blood*. 2014;124:1503.
41. Tuinenburg A, Biere-Rafi S, Peters M, et al. Obesity in haemophilia patients: effect on bleeding frequency, clotting factor concentrate usage, and haemostatic and fibrinolytic parameters. *Haemophilia*. 2013;19:744–752.
42. Majumdar S, Ahmad N, Karlson C, Morris A, Iyer R. Does weight reduction in haemophilia lead to a decrease in joint bleeds? *Haemophilia*. 2012;18:e82–e84.
43. Yerrabothala S, McKernan L, Ornstein DL. Bariatric surgery in haemophilia. *Haemophilia*. 2016;22:e232–e234.
44. Sousos N, Gavriilaki E, Vakalopoulou S, Garipidou V. Understanding cardiovascular risk in hemophilia: a step towards prevention and management. *Thromb Res*. 2016;140:14–21.
45. Humphries TJ, Ma A, Kessler CM, Kamalakar R, Pocoski J. A second retrospective database analysis confirms prior findings of apparent increased cardiovascular comorbidities in hemophilia A in the United States. *Am J Hematol*. 2016;91:E298–E299.
46. Pocoski J, Ma A, Kessler CM, Boklage S, Humphries TJ. Cardiovascular comorbidities are increased in US patients with haemophilia A: a retrospective database analysis. *Haemophilia*. 2014;20:472–478.
47. Ragni MV, Nichols LA. Ischemic heart disease mortality and coronary atherosclerosis in hemophilia. *Blood*. 2007;110:3192.
48. Sharathkumar AA, Soucie JM, Trawinski B, Greist A, Shapiro AD. Prevalence and risk factors of cardiovascular disease (CVD) events among patients with haemophilia: experience of a single haemophilia treatment centre in the United States (US). *Haemophilia*. 2011;17:597–604.
49. Siboni SM, Mannucci PM, Gringeri A, et al. Health status and quality of life of elderly persons with severe hemophilia born before the advent of modern replacement therapy. *J Thromb Haemost*. 2009;7:780–786.
50. Wang JD, Chan WC, Fu YC, et al. Prevalence and risk factors of atherothrombotic events among 1054 hemophilia patients: a population-based analysis. *Thromb Res*. 2015;135:502–507.
51. Biere-Rafi S, Baarslag MA, Peters M, et al. Cardiovascular risk assessment in haemophilia patients. *Thromb Haemost*. 2011;105:274–278.
52. Bilora F, Dei Rossi C, Girolami B, et al. Do hemophilia A and von Willebrand disease protect against carotid atherosclerosis? A comparative study between coagulopathics and normal subjects by means of carotid echo-color Doppler scan. *Clin Appl Thromb Hemost*. 1999;5:232–235.
53. Foley CJ, Nichols L, Jeong K, Moore CG, Ragni MV. Coronary atherosclerosis and cardiovascular mortality in hemophilia. *J Thromb Haemost*. 2010;8:208–211.
54. Fransen van de Putte DE, Fischer K, Makris M, et al. Unfavourable cardiovascular disease risk profiles in a cohort of Dutch and British haemophilia patients. *Thromb Haemost*. 2013;109:16–23.
55. Fransen van de Putte DE, Fischer K, Makris M, et al. Increased prevalence of hypertension in haemophilia patients. *Thromb Haemost*. 2012;108:750–755.

56. Sait AS, Kuo A, Bettencourt R, Bergstrom J, Allison M, von Drygalski A. Risk assessment for coronary heart disease in patients with haemophilia: a single centre study in the United States. *Haemophilia*. 2014;20:763–770.
57. von Drygalski A, Kolaitis NA, Bettencourt R, et al. Prevalence and risk factors for hypertension in hemophilia. *Hypertension*. 2013;62:209–215.
58. Bilora F, Zanon E, Petrobelli F, et al. Does hemophilia protect against atherosclerosis? A case-control study. *Clin Appl Thromb Hemost*. 2006;12:193–198.
59. Blanchette VS, Shapiro AD, Liesner RJ, et al. Plasma and albumin-free recombinant factor VIII: pharmacokinetics, efficacy and safety in previously treated pediatric patients. *J Thromb Haemost*. 2008;6:1319–1326.
60. Henrard S, Hermans C. Impact of being overweight on factor VIII dosing in children with haemophilia A. *Haemophilia*. 2016;22:361–367.
61. Boban A, Henrard S, Lambert C, Hermans C. Continuous infusion of factor VIII concentrates in obese patients with severe haemophilia A: is weight-based dose-adjustment required? *Haemophilia*. 2016;22:e62–e64.
62. Graham A, Jaworski K. Pharmacokinetic analysis of anti-hemophilic factor in the obese patient. *Haemophilia*. 2014;20:226–229.
63. Alamuddin N, Wadden TA. Behavioral treatment of the patient with obesity. *Endocrinol Metab Clin North Am*. 2016;45:565–580.
64. Martinez-Gonzalez MA, Bes-Rastrollo M. Dietary patterns, Mediterranean diet, and cardiovascular disease. *Curr Opin Lipidol*. 2014;25:20–26.
65. National Hemophilia Foundation. Playing it safe: bleeding disorders, sports, and exercise. 2005.
66. Goto M, Takedani H, Yokota K, Haga N. Strategies to encourage physical activity in patients with hemophilia to improve quality of life. *J Blood Med*. 2016;7:85–98.
67. Souza JC, Simoes HG, Campbell CS, Pontes FL, Boullosa DA, Prestes J. Haemophilia and exercise. *Int J Sports Med*. 2012;33:83–88.
68. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19:e1–e47.
69. Barlow SE. Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics*. 2007;120(Suppl 4):S164–S192.
70. Spear BA, Barlow SE, Ervin C, et al. Recommendations for treatment of child and adolescent overweight and obesity. *Pediatrics*. 2007;120(Suppl 4):S254–S288.
71. Kulkarni R, Carlson L, Malouin RA, et al. Telehematology: expanding comprehensive care for pediatric patients with blood disorders through telemedicine at several delivery sites (medical homes, hospital clinics, home setting and hemophilia treatment centers (HTC)) and with interdisciplinary providers. *Blood*. 2015;126:5576.
72. Adams E, Deutsche J, Okoroh E, et al. An inventory of healthy weight practices in federally funded haemophilia treatment centres in the United States. *Haemophilia*. 2014;20:639–643.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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