








# Effectiveness of physical exercise on postural balance in patients with haemophilia: A systematic review

Ana Chimeno-Hernández<sup>1,2</sup>  | Felipe Querol-Giner<sup>1,2</sup>  | Sofía Pérez-Alenda<sup>1,2</sup>  |  
Rodrigo Núñez-Cortés<sup>1,3</sup>  | Carlos Cruz-Montecinos<sup>1,3,4</sup>  | Juan J. Carrasco<sup>1,2,5</sup>  |  
Marta Aguilar-Rodríguez<sup>2</sup> 

<sup>1</sup>Physiotherapy in Motion. Multispecialty Research Group (PTinMOTION), Department of Physiotherapy, University of Valencia, Valencia, Spain

<sup>2</sup>Department of Physiotherapy, University of Valencia, Valencia, Spain

<sup>3</sup>Department of Physical Therapy, Faculty of Medicine, University of Chile, Santiago, Chile

<sup>4</sup>Division of Research, Development and Innovation in Kinesiology, Kinesiology Unit, San José Hospital, Santiago, Chile

<sup>5</sup>Intelligent Data Analysis Laboratory, University of Valencia, Valencia, Spain

## Correspondence

Sofía Pérez-Alenda, Department of Physiotherapy, University of Valencia, C/ Gascó Oliag N 5, 46010 Valencia, Spain.  
Email: [sofia.perez-alenda@uv.es](mailto:sofia.perez-alenda@uv.es)

## Abstract

**Introduction:** Balance training is important to improve balance and to decrease the risk of falls in patients with haemophilia (PWH).

**Aim:** To analyse the current knowledge about the effectiveness of physical exercise on postural balance in PWH.

**Methods:** A systematic search for clinical trials, published before November 2021, was conducted using the following electronic databases: PubMed/MEDLINE, Web of Science, Embase, Wiley Online Library and the Cochrane Central Register of Controlled Trials (CENTRAL). Two independent reviewers extracted the data and assessed the risk of bias. The certainty of the evidence was analyzed using GRADE.

**Results:** A total of ten studies involving 304 patients were included. The studies performed strength and balance exercises, and some included flexibility, mobilization, and/or aerobic exercises in their training programs. Postural balance was evaluated using a force platform and the one leg stand test was the most frequently used. Only five exercise programs achieved a significant increase in balance (pre-post) with a strength, postural balance, flexibility, and aerobic intervention. In general, the quality rate of the risk of bias was fair but the overall quality of the evidence across the studies was very low.

**Conclusion:** Five studies showed that there is a positive change in balance after the intervention. However, there is currently an unclear demonstration of evidence for the use of physical exercises to improve postural balance in people with haemophilia. Further studies with a higher methodological quality are needed.

## KEYWORDS

balance exercises, haemophilia, physical therapy, postural control, therapeutic exercises

## 1 | INTRODUCTION

Haemophilia is a hereditary bleeding disorder characterized by a deficiency of coagulation factor VIII (haemophilia A) and factor IX (haemophilia B).<sup>1</sup> Despite being a rare disease, there are approximately 1,125,000 patients with haemophilia (PWH) worldwide with a prevalence of 17/4 (A/B) per 100,000 males.<sup>1,2</sup>

The iron accumulation caused by recurrent intra-articular (80%) bleedings typical of this disease induces synovial changes, cartilage damage, and bone alterations.<sup>3-5</sup> In PWH, the joint damage may affect the joint range of motion, muscle strength, and the proprioceptive system with the consequent alteration in postural balance.<sup>1,6-12</sup>

Imbalance could increase the risk of falls and kinesiophobia in this population.<sup>13</sup> Moreover, it could perpetuate the vicious cycle of sedentary lifestyle, worsening the musculoskeletal condition, and increasing the risk of bleedings and the health costs.<sup>14-16</sup> Physical exercise becomes a vital factor to stop this negative circle, and protect the joints in PWH.<sup>1,13,17,18</sup> The most used physical exercise programs in PWH include the proprioceptive and balance training beside flexibility, strength, and overall function (incorporating aerobic exercise).<sup>11,12,19</sup>

Recent systematic reviews have shown that physical exercise is safe and effective for improving different types of muscle strength in PWH.<sup>20-22</sup> However, the effects of physical exercise to improve balance have been little studied. For example, in the Strike et al.<sup>22</sup> systematic review, balance is a secondary aim and only one of the analyzed studies considered balance as a main outcome on a 30 children sample without arthropathy. Nevertheless, to our knowledge, there have been no subsequent reviews on the effects of physical exercise on PWH balance in other age ranges, with and without arthropathy.

Consequently, the aim of this review is to analyse the current knowledge of the effectiveness of physical exercise on balance in PWH.

## 2 | METHODS

### 2.1 | Protocol and registration

The protocol was registered in the International Prospective Register of Systematic Reviews PROSPERO (registration number: CRD42020215490) in December 2020. The reporting was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations.<sup>23</sup>

### 2.2 | Eligibility criteria

Randomized controlled trials (RCTs), controlled intervention studies and Before-After (Pre-Post) studies that analyzed the effects of a physical exercises programme on balance (measured by an instrumental assessment or clinical test) in PWH, with any age and type of severity, were included. The articles had to be written in the English language and published before November 2021. All editorials, letters to the edi-

tor, review articles, systematic reviews, meta-analyses, and in vivo and in vitro studies were excluded.

### 2.3 | Search strategy

The systematic search of clinical trials was conducted using the following electronic databases: PubMed/MEDLINE, Web of Science, Embase, Wiley Online Library and the Cochrane Central Register of Controlled Trials (CENTRAL). Articles with the following keywords were extracted and considered for inclusion: 1) For population: haemophilia OR hemophilia OR haemophilic arthropathy; 2) For intervention: therapeutic exercise OR balance exercise OR exercises OR physical therapy OR physical activity OR physiotherapy; 3) For primary outcome: balance OR postural control OR postural stability OR proprioception. We incorporated the use of Boolean operators (AND, OR, NOT) in the systematic search. In addition, a manual search of the included article references was conducted. All references were analyzed using Rayyan web software.<sup>24</sup>

### 2.4 | Study selection

Two authors (ACH, RNC) reviewed the abstracts and titles of all articles identified using the search strategy and any discrepancies were resolved by consensus. References considered not to be relevant were removed. Two authors (ACH, CCM) then independently evaluated the full articles to select those that met the eligibility criteria. If there were any differences between them, they were determined by a third reviewer (MAR).

### 2.5 | Data collection

A standardized data extraction table was developed using the Microsoft Excel template. Two reviewers (ACH, FQG) completed data extraction using a standardized form including the author and year of publication, study design, study population (participants and age), variables and measures, interventions, and results. In the case of disagreements, in any phase of the selection process, a third reviewer (MAR) made the decision.

### 2.6 | Evaluation and risk of bias rating

Two independent reviewers (ACH, FQG) assessed the risk of bias and the quality of the interventional studies using the tools recommended by the National Heart, Lung and Blood Institute.<sup>25</sup> The tool for the quality assessment of controlled intervention studies was made up of 14 questions covering the following topics: (1) Described as randomized; (2 and 3) treatment allocation—two interrelated pieces; (4 and 5) blinding; (6) similarity of the groups at baseline; (7 and 8) dropout; (9) adherence; (10) avoid other interventions; (11) outcome measures

assessment; (12) power calculation; (13) prespecified outcomes, and (14) intention-to-treat analysis.

The quality assessment of the Before-After (Pre-Post) studies without control group tool<sup>26</sup> was made up of 12 questions with the following themes: (1) Study question; (2) eligibility criteria and study population; (3) study participants representative of the clinical population of interest; (4) all eligibility participants enrolled; (5) sample size; (6) intervention clearly describe; (7) outcome measures described; (8) blinding of the outcome assessors; (9) follow-up rate; (10) statistical analysis; (11) multiple outcome measures, and (12) group-level interventions and individual-level outcome efforts.

The results of these tools were divided in three levels based on the items rated with an affirmative answer:  $\geq 75\%$  = good, 50–75% = fair,  $< 50\%$  = poor. The concordance was calculated using Cohen's kappa coefficient.

## 2.7 | Methods of analysis

The data collected was analyzed using a narrative synthesis of the evidence. The level of confidence impact was carried out using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.<sup>27</sup> The GRADE system specifies four categories for the quality of evidence: high, moderate, low, and very low. GRADE is based on the study design (RCTs start with high quality, not RCTs start with a low quality), five reasons that likely decrease the quality of evidence (risk of bias, inconsistency, indirectness, imprecision, and publication bias), and three reasons that raise the quality (large effect, dose response and all plausible residual confounding). During rating, it may be downgraded based on the level criteria if it is deemed to have a serious risk (-1) or very serious risk (-2).

## 3 | RESULTS

### 3.1 | Study selection

The search strategy identified 335 articles. Once the duplicates were eliminated, 237 remained. Of these, 25 were selected for the full text review and 212 were excluded because they did not meet the eligibility criteria. Ten studies were included in the systematic review<sup>28–37</sup> (Figure 1). We observed a very high concordance between the reviewers when selecting the studies ( $\kappa = 0.809$ ,  $p < 0.001$ ).

### 3.2 | Study characteristics

A total of 304 PWH were included. Of these, 44.08% were children (aged 9–13)<sup>30,33,36,37</sup> and 55.92% were adults (aged 32–59).<sup>28,29,31,32,34,35</sup> The number of participants per study ranged from 8<sup>30</sup> to 52.<sup>34</sup> Regarding the severity of haemophilia, 48.35% were severe; 22.70% moderate; 0.66%, mild; 18.42% severe/moderate, and 9.87% mild/moderate. Two hundred and four subjects were on pro-

phylaxis and 64 on demand. The treatment regimen was not specified in 36 people (Table 1).<sup>29,34,35</sup> Following the GRADE assessment, eight articles<sup>28–32,34,35,37</sup> were rated as very low, one as low,<sup>33</sup> and another one as moderate (Table 2).<sup>36</sup>

### 3.3 | Intervention

The training periods ranged from 1<sup>36</sup> to 13<sup>30</sup> months. Three studies performed the intervention three sessions per week<sup>30,33,36</sup> and four studies in 2 sessions/week.<sup>28,31,34,37</sup> One study encouraged the participants to exercise on all days for 8 weeks,<sup>32</sup> with another doing five sessions per week for 16 weeks.<sup>29</sup> Only one study did not state the session frequency.<sup>35</sup> In all of the interventions, strength and balance were trained; 5 studies incorporated flexibility,<sup>28,30,32,33,35</sup> two studies include mobilization exercises<sup>34,36</sup> and one study included flexibility and mobilization exercises;<sup>37</sup> three studies contain gait training exercises<sup>29,33,36</sup> and in another, aerobic exercises were included.<sup>33</sup>

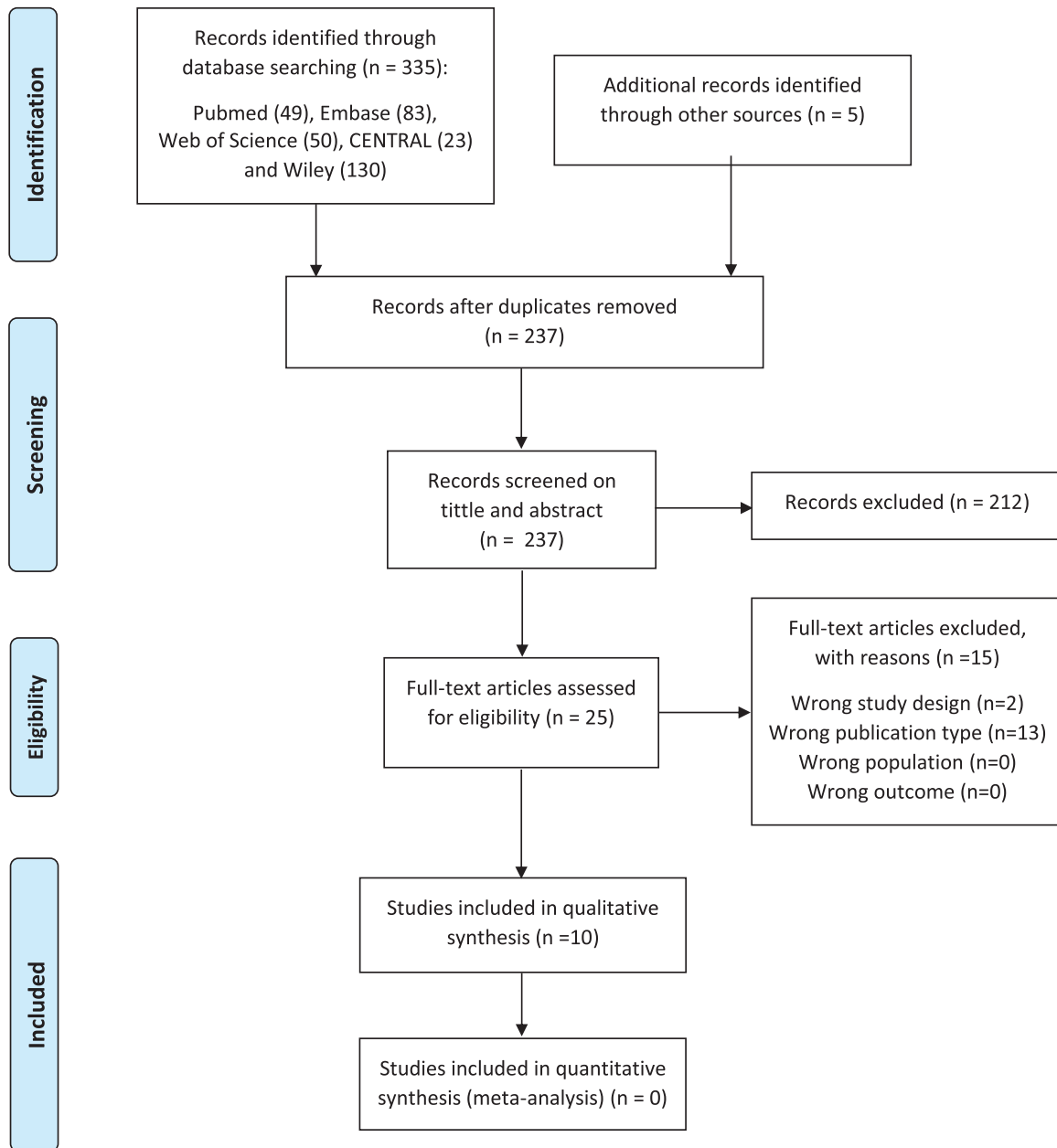
One study compared an exercise program with another physiotherapy intervention, specifically home exercising with a self-monitoring program (feedback and activity monitor) versus home exercising without an activity monitor.<sup>32</sup> Another study compared a combined exercise and laser protocol with a combined exercise and placebo protocol, specifically an active pulsed Nd:YAG laser and physical exercises versus placebo laser and physical exercises.<sup>36</sup> One study compared an exercise program with different aerobic training: treadmill versus bicycle ergometer.<sup>33</sup>

Three studies compared an exercises program versus a control group (normal life).<sup>31,34,37</sup> One study compared an exercise program in a intervention group of PWH with two control groups:<sup>28</sup> PWH and healthy subjects. Three studies analyzed the effect of an exercise program in PWH without a control group (Table 2).<sup>29,30,35</sup>

### 3.4 | Risk of bias

A very high concordance between the reviewers in the quality assessment was observed ( $\kappa = 0.881$ ,  $P < 0.001$ ). Table 3 shows the risk of bias for the controlled intervention studies using the tools recommended by the National Heart, Lung and Blood Institute.<sup>25</sup> The majority of the studies<sup>32–34,37</sup> had a fair quality rate of risk of bias; two<sup>28,31</sup> had a poor quality rate and one<sup>36</sup> had a good quality rate. Three out of seven<sup>28,32,37</sup> did not report whether the study was randomized or not. Only three studies<sup>32–34</sup> had an adequate method of randomization and simply one study had a good allocation concealment.<sup>36</sup> Six out of seven failed to report whether there was a blinding of the participants and providers. Three out of seven articles had a drop-out rate  $\geq 15\%$ .<sup>28,31,34</sup> However, there showed a high adherence (between 90% and 100%)<sup>31–34,36,37</sup> to the exercise program in six studies. Finally, all studies showed homogeneity across the groups at baseline.

Table 4 shows the risk of bias for the Before-After (Pre-Post) studies without control group using the Quality Assessment tool recommended by the National Heart, Lung and Blood Institute.<sup>26</sup> One<sup>29</sup> of



**FIGURE 1** Flowchart of the search studies and selection process

them had a good quality rate of risk of bias and the other two had a fair<sup>35</sup> and poor<sup>30</sup> quality rate respectively.

### 3.5 | Data synthesis

Table 5 describes the exercises, balance assessment and results. Regarding to the different interventions, four studies<sup>28,30,32,35</sup> combined a balance training with strength and flexibility exercise, which two<sup>28,32</sup> of them have statistically significant changes in balance (pre-post intervention) with  $P < 0.05$ . Two studies<sup>31,34</sup> combined a balance training with strength and joint mobilization exercise, without statistically significant changes in balance (pre-post intervention). One

study<sup>29</sup> combined a balance training with strength and walking exercise without statistically significant changes in balance (pre-post intervention). Another study<sup>33</sup> combined balance training with strength, flexibility, gait exercise, and aerobic exercise, with statistically significant changes in balance (pre-post intervention) with  $p < 0.05$ . One study<sup>37</sup> combined balance training with strength, flexibility, joint mobilization, neuromuscular control, and gait exercise with statistically significant changes in balance (pre-post intervention) with  $p < 0.05$ . Finally, one study<sup>36</sup> combined balance training with strength, joint mobility, and gait exercise with statistically significant changes in balance (pre-post intervention) with  $p < 0.05$ .

For the balance assessment, different measurements were carried out. Four studies used the one-leg stance test,<sup>28,30,31,34</sup> five studies

**TABLE 1** Patients characteristics of the included studies

Author	Disease severity	Type haemophilia	Population	Mean age	Factor therapy	Affected joint	n
Hilberg et al. <sup>28</sup> 2003	Severe (9)	A	Adult	IG: 32.4±9.4 ACH: 36.4±8.7 PCH: 34.2±8.2	Prophylaxis	IG: 8 ankles and 6 knee severely affected. 6 ankles and 8 knees moderately affected. 2 ankles and 2 knees mildly affected. 2 ankles and 2 knees not affected	28
Hill et al. <sup>29</sup> 2010	Severe (9), moderate (2) and mild (1)	A (11), B (1)	Adult	IG: 40.9	NA	NA	12
Pierstorff et al. <sup>30</sup> 2011	Severe (4), moderate (3) and mild (1)	A	Children	IG: 9.4	Prophylaxis (6) On demand (2)	IG: 8 ankle target joint; 7 knee target joint	8
Czepa et al. <sup>31</sup> 2013	Severe (25)	A (24), B (1)	Adult	IG: 45±5 CG: 36±15 HC: 39±11	Prophylaxis (12) On demand (13)	NA	44
Goto et al. <sup>32</sup> 2014	Severe (27), moderate (5)	A (26), B (6)	Adult	IG: 41.8±8.6 CG: 43.9±10.7	Prophylaxis (25) On demand (7)	<b>Grade 0-II/IV-V arthropathy (Arnold-Hilgartner classification):</b> IG: Grade 0-III (5 knee and 2 ankles); Grade IV-V (6 knee and 13 ankles); 5 knee arthroplasty; 1 ankle arthroplasty CG: Grade 0-III (5 knee and 4 ankles); Grade IV-V (6 knee and 12 ankles); 5 knee arthroplasty	32
Mohamed et al. <sup>33</sup> 2015	Mild/moderate (30)	NA	Children	IG: Group A 12.4±1.4; Group B 12.8±1.4	On demand	Without arthropathy	30
Runkel et al. <sup>34</sup> 2016	Severe (47), moderate (5)	A, B	Adult	IG: 41.9±10.6 CG: 40.3±8.8	Prophylaxis (42) On demand (4) NA (6)	<b>Gilbert (mean, SD)</b> IG: ankle left: 4.1, 1.5; ankle right: 4.2, 1.5; knee left: 2.3, 1.6; knee right: 2.5, 1.7. CG: ankle left: 4.2, 1.9; ankle right: 3.9, 1.6; knee left: 2.1, 1.5; knee right: 1.6, 1.4.	52
Boccalandro et al. <sup>35</sup> 2017	Severe (26), moderate (14)	A (38), B (2)	Adult	IG: 59.6±9.1	Prophylaxis (14) On demand (8) NA (18)	35 patients with arthropathy	40
Elmaggar et al. <sup>36</sup> 2018	Severe and moderate (56)	A	Children	IG: 8.7±1.4 HC: 8.4±1.3	Prophylaxis	IG: inclusion criteria = ankle joint with grade II-III arthropathy (Arnold-Hilgartner classification)	79
Elmaggar et al. <sup>37</sup> 2020	Moderate (40)	A	Children	IG: 12.2±2.4 CG: 11.6±2	Prophylaxis	<b>Grade II/III arthropathy (Arnold-Hilgartner classification)</b> Grade II: 24 ankles, Grade III: 11 ankles; Right Ankle: 26, Left ankle: 9	40

Abbreviations: IG: interventional group; CG: control group; ACH: active control healthy; PCH: passive control healthy; HC: healthy control; NA: not available.



TABLE 2 Data extraction and GRADE

Author	Design	Participants	Intervention	Outcomes	GRADE
Hilberg et al. <sup>28</sup> 2003	Pretest-posttest study with two control group	PWH: 9 (32.4 ± 9.4) ACH: 8 (36.4 ± 8.7) PCH: 11 (34.2 ± 8.2)	PwH and ACH: 6-months Programme training (2 days/week) (60 min/day): strength (limbs and ankle), flexibility and proprioception. PCH: normal lives.	Isometric strength: knee extensor and leg press. Balance: one-leg stance and posturomed test. ROM: angle reproduction test. Vibration sensation: turning fork test.	Very low⊕
Hill et al. <sup>29</sup> 2010	Pretest-posttest study without control group	IG: 12 (40.9 [32.9-48.9])	IG: 4-month individualize home exercises (5 days /week) 6-8 exercises: Balance, strength and walk. No control group.	Functionality: TUG, STST, step test, functional reach test. Balance (Neurocom balance system): mCTSIB, LoS, walking, step quick turn. Strength (Quadriceps) mFESHuman activity profile	Very low⊕
Pierstorff et al. <sup>30</sup> 2011	Pretest-posttest study without control group	IG: 8 children (9.4)	IG: 13-month exercises programme (3 days/week) (30 min/day): train strength, flexibility and stability. No control group.	Balance: one-leg stance (OE, CE), standing on a balance board and roll a softball using both feet. Flexibility: finger to floor distance.	Very low⊕
Czepa et al. <sup>31</sup> 2013	Pretest-posttest study with two control groups	IG: 13 (45 ± 5) CG: 12 (36 ± 15) HC: 19 (39 ± 11)	Active PwH: 12-month training program (2 days/week): muscle tone regulation, mobilization and muscle activation and holistic therapeutic techniques. Passive PwH and Healthy: normal lives.	Objective physical performance: one-leg stand, ROM, 12 min-walk, Borg scale, Visual analogue scale (VAS). Subjective physical performance: Hep-Test-Q questionnaire. Activity level (Linkert scale)	Very low⊕
Goto et al. <sup>32</sup> 2014	RCT	IG: 16 (41.8 ± 8.6) CG: 16 (43.9 ± 10.7)	IG: 2-months Home exercise programme with self-monitoring programme (7 days/week): strength knee extension, static stretching knee flexor muscle, standing balance training and walking. CG: home exercise with undisplayed activity monitor.	Balance: modified-Functional Reach Test and 10 min gate time. Pain (VAS). Strength (hand-held dynamometer). Self-efficacy exercises (Modified Marcus Scale OKA). Adherence (%). Physical activity: accelerometer.	Very low⊕
Mohamed et al. <sup>33</sup> 2015	RCT	IG: Group A 15 (12.4 ± 1.4); Group B 15 (12.8 ± 1.4)	Both: 3-months Physical exercise programme (3 days/week) (60 min/day): isometric, stretching, balance and aerobic exercise (Group A bicycle ergometer; Group B treadmill).	Balance (Biodex Stability and Gait Trainer System): static balance stable and unstable (AP and ML stability). Walk gait parameters: time on each foot (%), average step length (meter) and average step cycle (cycle/second).	Low⊕⊕

(Continues)



TABLE 2 (Continued)

Author	Design	Participants	Intervention	Outcomes	GRADE
Runkel et al. <sup>34</sup> 2016	RCT	IG: 24 (41.9 ± 10.6) CG: 28 (40.3 ± 8.8)	IG: 6-months training program (2 days/week) (90 min/day): mobility, coordination, strength and endurance. CG: normal lives.	<b>Balance:</b> one-leg stand. <b>Strength:</b> mobile strength sensor (triceps, biceps, latissimus dorsi, rectus abdominis, quadriceps and triceps femoris). <b>Functionality:</b> 12 min walk test. <b>Joint health:</b> Gilbert test.	Very low⊕
Boccalandro et al. <sup>35</sup> 2017	Pretest-posttest study without control group	IG: 40 (59.6 ± 9.1)	IG: 12-month study with 9-months training program: balance, flexibility, strength and resistant training. No control group.	<b>Balance:</b> force platform (sway area, velocity and the centre of force trajectory) and Tinetti scale. <b>Joint health:</b> HJHS. <b>Pain (VAS):</b> <b>Physical activity and normal daily functions:</b> HAL, IADL, ADL. <b>Emotional status:</b> SF-36, Health Assessment Questionnaire, Global Health status and Beck scale.	Very low⊕
Elmaggar et al. <sup>36</sup> 2018	Pretest-posttest study with two control groups	IG: 8.7 ± 1.4; HC: 8.4 ± 1.3	IG: 6 weeks training program (2 days/week): pain and swelling relief, flexibility, strength, proprioception and neuromuscular control. <b>Healthy control:</b> normal lives.	<b>Balance:</b> force platform (A-P stability index, M-L stability index and Overall stability index). <b>Strength:</b> manual muscle test. <b>ROM:</b> Electro goniometer. <b>Pain:</b> VAS scale. <b>Pedobarography:</b> static foot print (foot length, width and foot form index) and dynamic loading test (foot pressure).	Very low⊕
Elmaggar et al. <sup>37</sup> 2020	RCT	IG: 20 (12.2 ± 2.4) CG: 20 (11.6 ± 2)	<b>Both:</b> one-month training program (3 days/week) (30 min/day): mobilization, strength, balance and gait exercises. <b>IG:</b> treatment with pulsed Nd:YAG laser; <b>CG:</b> treatment with placebo light.	<b>Pain:</b> numerical pain rating scale. <b>Postural control (NeuroCom Balance system):</b> LoS test. <b>weight-bearing pattern (Tekscan HR Mat™ Barefoot Pressure Mapping System).</b>	Moderate⊕⊕

Abbreviations: RCT: randomized clinical trial; CT: clinical trial; IG: interventional group; CG: control group; ACH: active control healthy; PCH: passive control healthy; HC: healthy control; ROM: range of motion; TUG: time up and go; STST: sit to stand test; mCTSIB: modified clinical test of sensory interaction in balance; mFES: modified fall efficacy scale; HJHS: haemophilia joint health score; HAL: haemophilia activity list; IADL: instrumental activities of daily living and ADL: activities of daily living; VAS: visual analogue scale; LoS: limits of stability.

**TABLE 3** Quality of included studies assessed through the National Heart, Lung and Blood Institute risk of bias tool

Year	Author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	TotalScore	Quality Rating
2020	Elnaggar et al. <sup>37</sup>	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	12/14 (85.71%)	Good
2018	Elnaggar et al. <sup>36</sup>	NR	NR	NR	NR	NR	Y	Y	Y	Y	Y	Y	NR	Y	Y	8/14 (57.14%)	Fair
2016	Runkel et al. <sup>34</sup>	Y	Y	NR	NR	NR	Y	Y	N	Y	Y	Y	NR	Y	N	8/14 (57.14%)	Fair
2015	Mohamed et al. <sup>33</sup>	Y	Y	N	Y	NR	Y	Y	Y	Y	Y	Y	N	Y	NR	10/14 (71.43%)	Fair
2014	Goto et al. <sup>32</sup>	Y	Y	NR	NR	N	Y	Y	Y	Y	Y	Y	N	Y	N	9/14 (64.29%)	Fair
2013	Czepa et al. <sup>31</sup>	NR	NR	NR	NR	NR	Y	N	N	Y	Y	Y	N	Y	N	5/14 (35.71%)	Poor
2003	Hilberg et al. <sup>28</sup>	NR	NR	NR	NR	NR	Y	Y	N	NR	Y	Y	N	Y	NR	5/14 (35.71%)	Poor

**Quality Assessment of Controlled Intervention Studies.** 1. Was the study described as randomized, a randomized clinical trial, or an RCT? 2. Was the method of randomization adequate (i.e., use of randomly generated assignment)? 3. Was the treatment allocation concealed (so that assignments could not be predicted)? 4. Were study participants and providers blinded to treatment group assignment? 5. Were the people assessing the outcomes blinded to the participants' group assignments? 6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)? 7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment? 8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower? 9. Was there high adherence to the intervention protocols for each treatment group? 10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)? 11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants? 12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power? 13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)? 14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis? **Total Score:** Number of yes; **CD,** cannot be determined; **NA,** not applicable; **NR,** not reported; **N,** no; **Y,** yes. **Quality Rating:** Poor <50%, Fair 50–75%, Good ≥75%.

**TABLE 4** Quality of included studies assessed through the National Heart, Lung and Blood Institute risk of bias tool

Year	Author	1	2	3	4	5	6	7	8	9	10	11	12	TotalScore	Quality Rating
2017	Boccalandro et al. <sup>35</sup>	Y	Y	N	NR	NR	Y	Y	N	Y	Y	N	Y	7/12 (58.33%)	Fair
2011	Pierstoff et al. <sup>30</sup>	Y	N	N	NR	N	Y	Y	N	N	Y	N	Y	5/12 (41.66%)	Poor
2010	Hill et al. <sup>29</sup>	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	Y	9/12 (75%)	Good

**Quality Assessment for Before-After (Pre-Post) Studies with No Control Group.** 1. Was the study question or objective clearly stated? 2. Were eligibility/selection criteria for the study population prespecified and clearly described? 3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest? 4. Were all eligible participants that met the prespecified entry criteria enrolled? 5. Was the sample size sufficiently large to provide confidence in the findings? 6. Was the test/service/intervention clearly described and delivered consistently across the study population? 7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants? 8. Were the people assessing the outcomes blinded to the participants' exposures/interventions? 9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis? 10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to- post changes? 11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)? 12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level? **Total Score:** Number of yes; **CD,** cannot be determined; **NA,** not applicable; **NR,** not reported; **N,** no; **Y,** yes. **Quality Rating:** Poor <50%, Fair 50–75%, Good ≥75%.



TABLE 5 Exercises, balance assessment and results

Author	Types of physical exercise	Balance assessment	Results
Hilberg et al. <sup>28</sup> 2003	<b>Strength:</b> lower limbs, ankle, foot (short foot by Janda) and hip. <b>Flexibility:</b> PIR. <b>Balance:</b> hard and soft surfaces. At the end they use step, togu and mini-trampoline. (No specific exercises are described).	<b>Balance:</b> one-leg stance (OE/CE)-hard/soft surface) and posturomed test.	<b>One-leg stance (OE/CE-hard/soft surface):</b> improved after the program ( $p < 0.05$ ) in IG and ACH. <b>Posturomed test:</b> IG the resettling time change (1.61-1.21) but was not significant. The different of resettling time mean of ACH and PCH was significant ( $p < 0.05$ ). Strength, balance and turning fork test have significant changes ( $p < 0.05$ ).
Hill et al. <sup>29</sup> 2010	<b>Strength (lower limbs) and walking programme.</b> The exercises were selected from: The Otago exercises program. <b>Balance:</b> The exercises were selected from: Health promotion resources balances and vestibular exercises kit (milder levels), (no specific exercises are described).	<b>Balance (Neurocom balance system):</b> mCTSIB, LoS, walking, step quick turn.	<b>Balance:</b> non-significant improvement.
Pierstorff et al. <sup>30</sup> 2011	<b>Strength and flexibility</b> <b>Balance:</b> tailored program exercises. They use a balance board and two softballs. (no specific exercises are described).	<b>Balance:</b> one-leg stance (OE, CE), standing on a balance board and roll a softball using both feet.	<b>Balance:</b> slight improvement in one-leg stance and the other two test but not significant changes.
Czepa et al. <sup>31</sup> 2013	<b>Muscle tone regulation:</b> PIR, myofascial release techniques, stretching. <b>Muscle activation:</b> short foot by Janda, isometric resistance exercises, dynamic low resistance exercise using Thera-Band® and knee bend. <b>Joint mobilization and body awareness:</b> regulation respiration, variation in centre of gravity. <b>Balance:</b> program sport therapy from the Haemophilia and exercises project. (no specific exercises are described).	<b>Balance:</b> one-leg stand.	<b>One-leg stance:</b> there are not changes.
Goto et al. <sup>32</sup> 2014	<b>Strength of knee extension training (10 times/day):</b> isometric exercise at a long-sitting position, resistive training at sitting position, a half squat with both legs at standing position and a half squat with a single leg at standing position. <b>Static stretching for knee flexor muscle (5 times/day):</b> tailored program. Moving the body's COG (AP-ML), stepping (AP) and standing balance exercises with a single leg. <b>Advice for the promotion of physical activity:</b> walking, leading an active life and doing non-contact sports were recommended.	<b>Strength of knee extension training (10 times/day):</b> isometric exercise at a long-sitting position, resistive training at sitting position, a half squat with both legs at standing position and a half squat with a single leg at standing position. <b>Static stretching for knee flexor muscle (5 times/day):</b> tailored program. Moving the body's COG (AP-ML), stepping (AP) and standing balance exercises with a single leg. <b>Advice for the promotion of physical activity:</b> walking, leading an active life and doing non-contact sports were recommended.	<b>Strength of knee extension training (10 times/day):</b> isometric exercise at a long-sitting position, resistive training at sitting position, a half squat with both legs at standing position and a half squat with a single leg at standing position. <b>Static stretching for knee flexor muscle (5 times/day):</b> tailored program. Moving the body's COG (AP-ML), stepping (AP) and standing balance exercises with a single leg. <b>Advice for the promotion of physical activity:</b> walking, leading an active life and doing non-contact sports were recommended.

(Continues)



TABLE 5 (Continued)

Author	Types of physical exercise	Balance assessment	Results
Mohamed et al. <sup>33</sup> 2015	<p><b>Stretching exercises:</b> biceps brachia, hamstrings and calf muscle bilaterally. (20" Strench-20"relax)</p> <p><b>Isometric muscle contraction:</b> quadriceps, hamstring, anterior tibial group, calf muscle, biceps and triceps. (5 rep/5"contraction -5"relax).</p> <p><b>Balance:</b> balance and gait training exercises with obstacles (Group A bicycle ergometer; Group B treadmill).</p>	<p><b>Stretching exercises:</b> biceps brachia, hamstrings and calf muscle bilaterally. (20" Strench-20"relax)</p> <p><b>Isometric muscle contraction:</b> quadriceps, hamstring, anterior tibial group, calf muscle, biceps and triceps. (5 rep/5"contraction -5"relax).</p> <p><b>Balance:</b> balance and gait training exercises with obstacles (Group A bicycle ergometer; Group B treadmill).</p>	<p><b>Stretching exercises:</b> biceps brachia, hamstrings and calf muscle bilaterally. (20" Strench-20"relax)</p> <p><b>Isometric muscle contraction:</b> quadriceps, hamstring, anterior tibial group, calf muscle, biceps and triceps. (5 rep/5"contraction -5"relax).</p> <p><b>Balance:</b> balance and gait training exercises with obstacles (Group A bicycle ergometer; Group B treadmill).</p>
Runkel et al. <sup>34</sup> 2016	<p><b>Strength:</b> biceps, triceps, quadriceps, biceps femoris, rectus abdominus and latissimus muscle.</p> <p><b>Mobility and endurance:</b> were adopted individually.</p> <p><b>Balance:</b> they use the Program sport therapy (PST) and 5-9 exercises (strength and balance) were specifically selected for every patient. (no specific exercises are described).</p>	<p><b>Balance:</b> one-leg stand.</p>	<p><b>The one-leg stand:</b> displayed a significant difference concerning the right side on a flat ground.</p>
Boccalandro et al. <sup>35</sup> 2017	<p><b>Strength:</b> isometric exercises (quadriceps).</p> <p><b>Flexibility</b></p> <p><b>Balance:</b> flexibility exercises to improve balance. (no specific exercises are described).</p>	<p><b>Balance:</b> force platform (sway area, velocity and the centre of force trajectory) and Tinetti scale.</p>	<p><b>The Tinetti scale:</b> no changes.</p> <p><b>Force platform:</b> improvement from phase 1 to phase 3 was observed with respect to the median acceleration of body sway (<math>p &lt; 0.05</math>)</p>
Elhaggar et al. <sup>36</sup> 2018	<p><b>Strength:</b> isometric dorsiflexors, simultaneous active hip flexion, knee flexion and ankle dorsiflexion, Theraband strengthening of ankle dorsiflexor, plantar flexor, evorlor and inverter muscles, mini squat, one leg mini squat and scissor hop.</p> <p><b>Mobility and flexibility:</b> passive ankle dorsi and plantar flexion, passive stretching of calf muscles, passive ankle dorsiflexion with oscillatory traction and compression, mobilisation of the tibiotalar and subtalar joints.</p> <p><b>Balance:</b> weight shift, bilateral stance oscillatory bouncing on a trampoline, single limb support (and catch a ball), bouncing on toes, balance board (two legs or one leg) and walking on balance beam.</p>	<p><b>Balance:</b> force platform (APSI, MLSI and OSI).</p>	<p><b>Balance:</b> significant reduction of AP stability, ML stability as well as the overall stability indices IG in comparison to HG (<math>p &lt; 0.05</math>).</p>
Elhaggar et al. <sup>37</sup> 2020	<p><b>Strength:</b> low-intense isometric strength training, dynamic strength training using Thera-Bands®.</p> <p><b>Mobilization:</b> passive and active ROM exercises (tibiotalar and subtalar joint mobilization).</p> <p><b>Balance:</b> balance, gait training and proprioceptive exercises. (no specific exercises are described).</p>	<p><b>Postural control (NeuroCom Balance system) LoS:</b> DC, EE, CoG MV and MXE.</p>	<p><b>Balance:</b> DC, EE and CoG MV have significant changes (<math>p &lt; 0.05</math>).</p>

Abbreviations: PIR: post isometric muscle relaxation; OE: open eyes; CE: close eyes; IG: interventional group; ACH: active control healthy; PCH: passive control healthy; HC: healthy control; mCTSIB: modified clinical test of sensory interaction in balance; LoS: limits of stability; TUG: time up and go; STST: sit to stand test; COG: center of gravity; AP: anteroposterior; ML: medio lateral; mFRT: modified-functional reach test; ROM: range of motion; 12MWT: 12minute walk test; APSI: AP stability index; MLSI: ML stability index; OSI: overall stability index; DC: directional control; EE: endpoint excursion; CoG MV: center of gravity movement velocity; MXE: composite maximum excursion.

used a force platform,<sup>29,33,35–37</sup> and three of them also used one or two complementary tests (Tinetti test<sup>35</sup> the modified functional reach test (mFRT),<sup>32</sup> the modified clinical test of sensory interaction in balance (mCTSIB),<sup>29</sup> and the step quick turn test<sup>29</sup>).

The one-leg stance test showed statistically significant changes in balance (pre-post intervention) with  $p < 0.05$  in two studies,<sup>28,34</sup> although in one of them,<sup>34</sup> his test showed significant changes only in the right leg balance. The force platform proved there to be a balance improvement (pre-post intervention) in the five studies but only in three of them<sup>33,36,37</sup> were the changes statistically significant. Balance, measured by the modified functional reach test, improved with significant statistical changes in one study.<sup>32</sup> In total, only five studies demonstrated a statistical significant increase in balance (pre-post intervention).<sup>28,32,33,36,37</sup>

## 4 | DISCUSSION

This review presents the current evidence of trials applying a variety of exercise programs with potential effects on balance in PWH. Although in five of the included studies there was a positive change in balance after the intervention, the analysis of the methodological quality of the cited studies showed unclear evidence.

In this systematic review, three of four articles showed there to be statistical significant changes in balance measured using a force platform in children.<sup>33,36,37</sup> All of them included in their training program strength, static postural balance, and gait exercises, and some of them included flexibility,<sup>33</sup> joint mobility,<sup>36,37</sup> aerobic exercises,<sup>33</sup> and neuromuscular control.<sup>37</sup> Moreover, one of these articles had a moderate quality of evidence in the GRADE analysis.<sup>36</sup> Regarding adults, two<sup>28,32</sup> of six articles demonstrated significant changes in balance. However, all of them had a very low quality of evidence in the GRADE analysis. It seems that balance tends to improve with an exercise program but it is unclear as to the type of exercises that can influence the improvements more.

We could cautiously interpret that strength and flexibility affect balance to a slight extent since these two types of exercises are integrated in all interventions but only five<sup>28,32,33,36,37</sup> showed statistically significant changes. This means that perhaps these two training methods along with other types of exercise (aerobic, resistance, or multimodal balance exercises) could have a greater effect on balance.

As indicated by Thomas et al.,<sup>38</sup> in their systematic reviews about balance and fall prevention in elderly, the evidence we found points to a combined program of exercises involving balance, strength, and endurance is effective to improving postural balance, while also promoting a reduced risk of falls in elderly.<sup>38</sup> Moreover, in the Physical Activity Guidelines for Americans, they claim that in addition to balance exercises, strength work on the trunk and legs muscles also increases balance and prevents falls.<sup>39</sup> Similarly, for other diseases such as ataxia,<sup>40</sup> Parkinson's<sup>41</sup> and osteoarthritis<sup>42,43</sup> and also in total knee replacements,<sup>44</sup> studies showed that balance and coordination can be improved not only by training using specific balance exercises but also with combined strength, aerobic (cycling or walk), or virtual reality exercises.

These statements are supported by the previous findings in the literature associated with the importance of physical exercise to maintain strong muscle and flexible joints, as well as preserving normal postural control and balance in PWH.<sup>17,22,45,46</sup>

Considering the heterogeneity of joint and motor impairment in PWH, it is necessary to supervise and individualize the exercise programs according to the needs of each person. This should be done by a healthcare professional who understands haemophilia, like Negrier et al.<sup>45</sup> and Souza et al.<sup>46</sup> reported. However, there is currently no homogeneity in the frequency and intervention duration to be applied in balance exercises. Sherrington et al.<sup>47</sup> and Lee et al.<sup>48</sup> suggested that at least in older adults, it is necessary to train balance one hour, twice a week. The exercises should aim to challenge balance in three ways: reducing the base of support, moving the center of gravity, and reducing the use of arms support. The American College of Sports Medicine (ACSM) suggests that older adults should train using balance exercises for a minimum of 2 to 3 day/week, for 20–30 minutes.<sup>49</sup> Frequency and intensity are still controversial issues in balance exercise programs.

Relating to postural balance, we should also consider the age factor. In children, motor development is influenced by the growth of the neuromuscular system, body proportions, and psychological characteristics.<sup>50,51</sup> Schedler et al.<sup>52</sup> affirmed that after balance training, healthy children seem to have a higher static balance and mobility compared to adolescents. We therefore cannot expect the same balance results in adults due to the biomechanical and neuromuscular differences between both groups.<sup>53</sup>

In the case of PWH, they may undergo an early alteration of the somatosensory system due to the intra-articular bleeding that they suffer with throughout their lives and the haemophilic arthropathy that they may develop, affecting their balance.<sup>54,55</sup> For this reason, it is essential to know the joint status of the ankles and knees before the intervention to more accurately recognize the effect of the exercise program on their balance. Unexpectedly, in our review, only three articles described in detail the severity or lack of arthropathy in their sample and four articles described the number of joints affected (Table 1). In future studies, it would be interesting to carry out a specific description of the affected joints with or without arthropathy, in order to know more precisely the effect of the exercise on balance regarding to the grade of arthropathy. Self-perceived functionality and the risk of falls are also important variables as part of understanding the degree of affection that bleeding causes in the joints and consequently in their stability.<sup>14,56–58</sup> Future studies on balance should examine these measures in PWH.

Overall, the reporting quality of many of the included studies was very poor. Only two studies rated highly when they were assessed for risk of bias. Many of them failed to provide details on the randomization or participant allocation as well as the blinding process. As is common in this population, the sample sizes were small with a maximum of 56 people. Due to the heterogeneity of the interventions (outcome measures and duration), sample sizes and people characteristics (age, haemophilic arthropathy, prophylaxis and severity of haemophilia), meta-analysis was not possible. This prevents being able to provide a firm recommendation on physical exercise to improve balance in PWH.

The systematic review had some limitations. Due to the scarce research in this population, we included randomized and non-randomized clinical trials, as well as non-controlled clinical trials. This reduces the quality of the trials and the significance of the results. However, this limitation underlines the difficulty of collecting data on PWH. A better design of clinical trials is required in this population. We suggest that further research should be undertaken in the following areas: general physical exercises and their effect on postural balance, postural balance and self-perceived functionality, or postural balance and the risk of falls.

## 5 | CONCLUSION

The finding of this systematic review point towards the idea that there is currently an unclear demonstration of evidence regarding the use of physical exercises to improve balance in PWH. The design of balance training programs that are evidence-based remains a challenge for physical therapists. This conclusion should inspire the creation of high-quality clinical trials to provide robust evidence.

## FUNDING INFORMATION

This research received no external funding.

## DISCLOSURES

The authors state that they have no interests which might be perceived as posing a conflict or bias.

## AUTHOR CONTRIBUTION

Ana Chimeno-Hernández participated in the study selection, data extraction, and risk of bias, and drafted the initial manuscript. Felipe Querol-Giner participated in the data extraction and risk of bias. Sofía Pérez-Alenda formulated the study concept, guided the study design and the project direction, provided content expertise and oversight to data analysis, and revised all versions of the manuscript. Rodrigo Núñez-Cortés and Carlos Cruz-Montecinos contributed to the study concept and participated in the study selection. Juanjo Carrasco participated in the data analysis and interpretation of the study selection. Marta Aguilar-Rodríguez formulated the study concept, guided the study design, participated in the data analysis, and revised all versions of the manuscript. All authors approved the final version of the manuscript.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## ORCID

Ana Chimeno-Hernández  <https://orcid.org/0000-0002-4449-0174>

Felipe Querol-Giner  <https://orcid.org/0000-0002-2590-284X>

Sofía Pérez-Alenda  <https://orcid.org/0000-0002-0841-5767>

Rodrigo Núñez-Cortés  <https://orcid.org/0000-0002-4068-9338>

Carlos Cruz-Montecinos  <https://orcid.org/0000-0002-3835-3368>

Juan J. Carrasco  <https://orcid.org/0000-0002-0740-3772>

Marta Aguilar-Rodríguez  <https://orcid.org/0000-0001-5541-0662>

## REFERENCES

1. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020;26(S6):1-158.
2. Iorio A, Stonebraker JS, Chambost H, et al. Establishing the prevalence and prevalence at birth of hemophilia in males: a meta-analytic approach using National Registries. *Ann Intern Med*. 2019;171(8):540.
3. Van Vulpen LFD, Holstein K, Martinoli C. Joint disease in haemophilia: Pathophysiology, pain and imaging. *Haemophilia*. 2018;24:44-49.
4. Zhu H, Meng Y, Tong P, Zhang S. Pathological mechanism of joint destruction in haemophilic arthropathy. *Mol Biol Rep*. 2021;48(1):969-74.
5. Vulpen LFD, Thomas S, Keny SA, Mohanty SS. Synovitis and synovectomy in haemophilia. *Haemophilia*. 2021;27(S3):96-102.
6. Barriuso R C. Effectiveness of Physiotherapy in the Treatment of Hemophilic Arthropathy a Systematic Review. *Ann Hematol Oncol*. 2017;4(9).
7. Lobet S, Hermans C, Lambert C. Optimal management of hemophilic arthropathy and hematomas. *J Blood Med*. 2014;207.
8. Hilberg T. Programmed Sports Therapy (PST) in People with Haemophilia (PwH) "Sports Therapy Model for Rare Diseases." *Orphanet J Rare Dis*. 2018;13(1):38.
9. Hilberg T, Herbsleb M, Gabriel HHW, Jeschke D, Schramm W. Proprioception and isometric muscular strength in haemophilic subjects. *Haemoph Off J World Fed Hemoph*. 2001;7(6):582-88.
10. Cruz-Montecinos C, De La Fuente C, Rivera-Lillo G, et al. Sensory strategies of postural sway during quiet stance in patients with haemophilic arthropathy. *Haemophilia*. 2017;23(5):e419-26.
11. Gallach JE, Querol F, González LM, Pardo A, Aznar JA. Posturographic analysis of balance control in patients with haemophilic arthropathy. *Haemophilia*. 2008;14(2):329-35.
12. Souza FMB, McLaughlin P, Pereira RP, et al. The effects of repetitive haemarthrosis on postural balance in children with haemophilia. *Haemophilia*. 2013;19(4):e212-17.
13. Forsyth AL, Quon DV, Konkole BA. Role of exercise and physical activity on haemophilic arthropathy, fall prevention and osteoporosis: EXERCISE AND PHYSICAL ACTIVITY IN HAEMOPHILIA. *Haemophilia*. 2011;17(5):870-76.
14. Sammels M, Vandesande J, Vlaeyen E, Peerlinck K, Milisen K. Falling and fall risk factors in adults with haemophilia: an exploratory study. *Haemophilia*. 2014;20(6):836-45.
15. Peel NM. Epidemiology of Falls in Older Age. *Can J Aging Rev Can Vieil*. 2011;30(1):7-19.
16. Siracuse JJ, Odell DD, Gondek SP, et al. Health care and socioeconomic impact of falls in the elderly. *Am J Surg*. 2012;203(3):335-38.
17. Gomis M, Querol F, Gallach JE, González LM, Aznar JA. Exercise and sport in the treatment of haemophilic patients: a systematic review. *Haemophilia*. 2009;15(1):43-54.
18. Timmer MA, Pisters MF, De Kleijn P, De Bie RA, Schutgens REG, Veenhof C. Movement behaviour in adults with haemophilia compared to healthy adults. *Haemophilia*. 2018;24(3):445-51.
19. Blamey G, Forsyth A, Zourikian N, et al. Comprehensive elements of a physiotherapy exercise programme in haemophilia - a global perspective: PHYSIOTHERAPY EXERCISE PROGRAMME IN HAEMOPHILIA. *Haemophilia*. 2010;16:136-45.
20. Wagner B, Krüger S, Hilberg T, et al. The effect of resistance exercise on strength and safety outcome for people with haemophilia: a systematic review. *Haemophilia*. 2020;26(2):200-215.
21. Siqueira TC, Dominski FH, Andrade A. Effects of exercise in people with haemophilia: an umbrella review of systematic reviews and meta-analyses. *Haemophilia*. 2019;25(6):928-37.
22. Strike K, Mulder K, Michael R. Exercise for haemophilia. Cochrane Cystic Fibrosis and Genetic Disorders Group, editor. *Cochrane Database Syst Rev*. 2016;12(12).
23. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that

- evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339(jul21 1):b2700-b2700.
24. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A Rayyan-a web and mobile app for systematic reviews. *Syst. Rev.* 2016;5:210.
  25. Quality assessment of controlled intervention studies. *Natl Heart Lung Blood Inst.* 2014.
  26. Quality assessment tool for before-after (Pre-Post) studies with no control group. *Natl Heart Lung Blood Inst.* 2014.
  27. Ryan R, Hill S. How to GRADE the quality of the evidence. *Cochrane Consum Commun Group.* 2016;Version 3.0.
  28. Hilberg T, Herbsleb M, Puta C, Gabriel HHW, Schramm W Physical training increases isometric muscular strength and proprioceptive performance in haemophilic subjects: PROPRIOCEPTIVE TRAINING IN HAEMOPHILICS. *Haemophilia.* 2003;9(1):86-93.
  29. Hill K, Fearn M, Williams S, et al. Effectiveness of a balance training home exercise programme for adults with haemophilia: a pilot study. *Haemophilia.* 2010;16(1):162-69.
  30. Pierstorff K, Seuser A, Weinspach S, Laws H-J Physiotherapy home exercise program for haemophiliacs. *Klin Pädiatr.* 2011;223(03):189-92.
  31. Czepa D, von Mackensen S, Hilberg T. Haemophilia & Exercise Project (HEP): The impact of 1-year sports therapy programme on physical performance in adult haemophilia patients. *Haemophilia.* 2013;19(2):194-99.
  32. Goto M, Takedani H, Haga N, et al. Self-monitoring has potential for home exercise programmes in patients with haemophilia. *Haemophilia.* 2014;20(2):e121-27.
  33. Mohamed RA, Sherief AEI-AA. Bicycle ergometer versus treadmill on balance and gait parameters in children with hemophilia. *Egypt J Med Hum Genet.* 2015;16(2):181-87.
  34. Runkel B, Czepa D, Hilberg T. RCT of a 6-month programmed sports therapy (PST) in patients with haemophilia - Improvement of physical fitness. *Haemophilia.* 2016;22(5):765-71.
  35. Boccacando E, Mancuso ME, Riva S, et al. Ageing successfully with haemophilia: a multidisciplinary programme. *Haemophilia.* 2018;24(1):57-62.
  36. Elnaggar RK. Pulsed Nd:YAG laser: effects on pain, postural stability, and weight-bearing pattern in children with hemophilic ankle arthropathy. *Lasers Med Sci.* 2020;35(5):1075-83.
  37. Elnaggar RK. Pedobarographic and stabilometric analysis and exercises for children with recurrent ankle haemarthrosis. *Int J Ther Rehabil.* 2018;25(9):481-92.
  38. Thomas E, Battaglia G, Patti A, et al. Physical activity programs for balance and fall prevention in elderly: A systematic review. *Medicine (Baltimore).* 2019;98(27):e16218.
  39. Piercy KL, Troiano RP, Ballard RM, et al. The physical activity guidelines for Americans. *JAMA.* 2018;320(19):2020-28.
  40. He M, Zhang H, Tang Z, et al. Balance and coordination training for patients with genetic degenerative ataxia: a systematic review. *J Neurol.* 2020.
  41. Mak MK, Wong-Yu IS, Shen X, Chung CL Long-term effects of exercise and physical therapy in people with Parkinson disease. *Nat Rev Neurol.* 2017;13(11):689-703.
  42. Levinger P, Dunn J, Bifera N, Butson M, Elias G, Hill KD High-speed resistance training and balance training for people with knee osteoarthritis to reduce falls risk: study protocol for a pilot randomized controlled trial. *Trials.* 2017;18(1):384.
  43. Takacs J, Krowchuk NM, Garland SJ, Carpenter MG, Hunt MA Dynamic balance training improves physical function in individuals with knee osteoarthritis: a pilot randomized controlled trial. *Arch Phys Med Rehabil.* 2017;98(8):1586-93.
  44. Blasco J-M, Acosta-Ballester Y, Martínez-Garrido I, García-Molina P, Igual-Camacho C, Roig-Casasús S The effects of preoperative balance training on balance and functional outcome after total knee replacement: a randomized controlled trial. *Clin Rehabil.* 2020;34(2):182-93.
  45. Negrier C, Seuser A, Forsyth A, et al. The benefits of exercise for patients with haemophilia and recommendations for safe and effective physical activity. *Haemophilia.* 2013;19(4):487-98.
  46. Souza J, Simoes H, Campbell CS, et al. Haemophilia and Exercise. *Int J Sports Med.* 2012;33(02):83-88.
  47. Sherrington C, Tiedemann A, Fairhall N, Close JCT, Lord SR Exercise to prevent falls in older adults: an updated meta-analysis and best practice recommendations. *New South Wales Public Health Bull.* 2011;22(4):78.
  48. Lee PG, Jackson EA, Richardson CR. Exercise Prescriptions in Older Adults. 2017;95(7):8.
  49. Garber CE, Blissmer B, Deschenes MR, et al. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc.* 2011;43(7):1334-59.
  50. Albert PT. Postural balance: understanding this complex mechanism. *Home Health Care Manag Pract.* 2013;25(6):279-81.
  51. Latorre Román PÁ, Mora López D, Robles Fuentes A, García Pinillos F Reference values of static balance in spanish preschool children. *Percept Mot Skills.* 2017;124(4):740-53.
  52. Schedler S, Brock K, Fleischhauer F, Kiss R, Muehlbauer T Effects of balance training on balance performance in youth: are there age differences?. *Res Q Exerc Sport.* 2020;91(3):405-14.
  53. Oba N, Sasagawa S, Yamamoto A, Nakazawa K, editor. Difference in postural control during quiet standing between young children and adults: assessment with center of mass acceleration *PLOS ONE.* 2015;10(10):e0140235.
  54. Deschamps K, Staes F, Eerdeken M, et al. Postural control during a transition task in haemophilic children, adolescents and young adults with haemophilic ankle arthropathy. *Haemophilia.* 2018;24(4):667-74.
  55. Fearn M, Hill K, Williams S, et al. Balance dysfunction in adults with haemophilia. *Haemophilia.* 2010.
  56. Brodin E, Hadzibajramovic E, Baghaei F, Sunnerhagen K, Nilsson Å Self-reported activity of Swedish persons with haemophilia: Change over 2.5 years. *J Rehabil Med.* 2018;50(7):643-51.
  57. Kuijlaars IAR, Emst M, Net J, Timmer MA, Fischer K Assessing the test-retest reliability and smallest detectable change of the haemophilia activities list. *Haemophilia.* 2021;27(1):108-12.
  58. Flaherty LM, Josephson NC. Screening for fall risk in patients with haemophilia. *Haemophilia.* 2013;19(3):e103-9.

**How to cite this article:** Chimeno-Hernández A, Querol-Giner F, Pérez-Alenda S, Núñez-Cortés R, Cruz-Montecinos C, Carrasco JJ, Aguilar-Rodríguez M. Effectiveness of physical exercise on postural balance in patients with haemophilia: A systematic review. *Haemophilia.* 2022;28:409–421. <https://doi.org/10.1111/hae.14556>