Received: 4 December 2020 | Revised: 30 September 2021 | Accepted: 12 October 2021

DOI: 10.1111/hae.14444

Haemophilia WILEY

ORIGINAL ARTICLE

Effects of a supervised therapeutic exercise program on musculoskeletal health and gait in patients with haemophilia: A pilot study

Volkan Deniz[1] | Nevin Atalay Guzel[1] | Sébastien Lobet[2,3,4] | Ali Bülent Antmen[5] | Hatice Ilgen Sasmaz[6] | Abdullah Kilci[7] | Omer Cumhur Boyraz[7] | Ozgür Gunaştı[8] | Sanli Sadi Kurdak[8]

[1] Department of Physiotherapy and Rehabilitation, Gazi University Faculty of Health Sciences, Ankara, Turkey

[2] Service d'hématologie, Cliniques universitaires Saint-Luc, Bruxelles, Belgium

[3] Université catholique de Louvain, Secteur des Sciences de la Santé, Institut de Recherche Expérimentale et Clinique, Neuromusculoskeletal Lab (NMSK), Brussels, Belgium

[4] Cliniques universitaires Saint-Luc, Secteur de kinésithérapie, Brussels, Belgium

[5] Department of Pediatric Hematology and Oncology, Acıbadem Hospital, Adana, Turkey

[6] Department of Pediatric Hematology, Çukurova University Faculty of Medicine, Adana, Turkey

[7] Faculty of Sport Sciences, Çukurova University, Adana, Turkey

[8] Division of Sport Physiology, Department of Physiology, Faculty of Medicine, Çukurova University, Adana, Turkey

Correspondence
Volkan Deniz, Gazi Universitesi, Saglik Bilimleri Fakultesi, Fizyoterapi ve Rehabilitasyon Anabilim Dalı, Emek mah. Biskek Cad. 6. Cad. No:206490 Çankaya Ankara, Turkey.
Email: volkand2014@gmail.com

Abstract

Introduction: Episodes of bleeding in patients with haemophilia (PwH) are associated with haemophilic arthropathy, limitations in physical performance, reduced quality of life (QoL), and gait disorders.

Aim: This non-randomized, controlled, interventional, prospective, single-centre pilot study aimed to assess the effects of an 8-week supervised therapeutic exercise program on musculoskeletal health, gait kinematic parameters (GKP), functional capacity, and QoL in adult PwH.

Methods: Nineteen PwH were allocated to an exercise group (n = 10) or a control group (n = 9). The patients in the exercise group followed an 8-week supervised therapeutic exercise program. The Haemophilia Joint Health Score (HJHS), a two-dimensional video-based gait kinematic analysis (2D-GKA), the 6-min walking test (6MWT), and the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-Qol) were used as the outcome measures at baseline, after the exercise program (at the 8th week), and at the 6th-month follow-up.

Results: A significant improvement was observed in the exercise group in the HJHS-Total and Haem-A-Qol Total scores and the 6MWT value after the exercise program. Moreover, the 2D-GKA revealed improvement in most of the GKP (knee extension during the midstance and late swing phases, ankle dorsiflexion during the midstance phase, and ankle plantar flexion during the preswing phase). However, the gain obtained by the exercise program was not maintained at the 6th-month follow-up for the HJHS-Total and Hem-A-QoL-Total scores and GKP.

Conclusion: The 8-week supervised therapeutic exercise program was successful in achieving improvement in joint health, GKP, functional capacity, and QoL in PwH.

KEYWORDS
arthropathy, exercise therapy, gait analysis, gait disorders, haemophilia, quality of life

1 | INTRODUCTION

Intra-articular bleeding (hemarthrosis) encountered in patients with haemophilia (PwH) causes hypertrophy of the synovium and damages the cartilages and thus leads to gradual joint destruction (haemophilic arthropathy). Joints that are affected by haemorrhages to the greatest extent are elbow, knee, and ankle joints.[1] Arthropathy due to recurrent bleeding causes disruption of the gait pattern in PwH.[2]

Gait is a complicated action consisting of spatiotemporal, kinetic, and kinematic parameters. Gait kinematic parameters (GKP) provide information about the range of motion (ROM) in the lower limb joints during walking.[2] Many studies have focused on identifying gait disorders in PwH using advanced gait analysis systems.[3–7] Three dimensional (3D) gait analyses have revealed likely changes in GKP in adult PwH with pre-existing arthropathy. In a previous study, decreased ankle ROM during the push-off phase and increased knee ROM during the swing phase were demonstrated in the presence of isolated bilateral or unilateral ankle arthropathy.[6] In another study by Lobet et al.,[7] significant decreases in the ankle and hip ROM were reported in the presence of multiple joint arthropathies.

It is now widely recognized that regular exercises are beneficial for PwH; however, there are studies reporting unchanged mobility scores[8] and joint status[9] in PwH with exercise programs. Moreover, to the best of our knowledge, there is no study conducted to investigate the effects of exercises on gait parameters in PwH in the literature.

Based on the above information, the present study aimed to investigate the effects of a regularly performed supervised therapeutic exercise program on the joint health, GKP, functional capacity, and QoL in adult PwH who had severe or moderate haemophilia as compared with a control group of adult PwH not attending a therapeutic exercise program. The hypothesis of the present study was as follows: therapeutic exercises may improve joint health, GKP and functional capacity and thereby QoL in PwH.

2 | MATERIALS AND METHODS

2.1 | Study design and participant selection and allocation

This pilot study was designed as a non-randomized, controlled, interventional, prospective, single-centre study with a follow-up period. This study was conducted in the Wellness Centre affiliated to Cukurova University between January 2020 and July 2020. Among 178 male PwH who were the members of a regional haemophilia association, those with haemophilia A or B, aged ≥18 years, having a confirmed arthropathy in the lower extremities (knee or ankle), and treated either by prophylaxis or on-demand were included. Patients with another congenital coagulopathy such as von Willebrand syndrome, those unable to walk due to haemophilic arthropathy, and those who developed inhibitors to FVIII or FIX were excluded.

Patients who were interested in participating in a therapeutic exercise program for an 8-week period were assigned to the exercise (intervention) group and those who could not regularly participate in the exercise program due to social reasons, time issues or lacking interest were assigned to the control group. This study was approved by the Clinical Research Ethics Committee of Cukurova University Medical Faculty (approval no: 89/55, date: 14.06.2019). All procedures were conducted according to the Declaration of Helsinki. The study protocol was registered in the clinicaltrials.gov (NCT04297696). Before initiation of the study, all patients were informed about the study protocol and provided written informed consent.

2.2 | Therapeutic exercise program

The patients in the exercise group followed an 8-week therapeutic exercise program consisting of two phases. The program included aerobic, proprioceptive, strengthening, and stretching exercises.[9,10] Aerobic exercises were performed using an elliptical bike. Proprioceptive exercises included balance training on one leg with visual support.[9] Strengthening exercises included low-intensity exercises to prevent excessive and deleterious compressive forces. Three intensity levels were determined based on the joint status and perception of pain.[10] Furthermore, an exercise band (yellow Theraband) was used to avoid likely injury risk due to the dropping of the free weights. Muscle stretching exercises were targeted to the hip flexors, quadriceps, hamstrings, and calves. Each stretch was performed in a gentle, low load, and prolonged manner within the pain-free range.[10] The properties of the therapeutic exercise program are summarized in Table 1. All patients completed each session by applying cryotherapy to the target joints in their lower extremities. Cryotherapy was applied for 15 min for each joint.[11]

The therapeutic exercises were performed 3 days a week in the gymnasium affiliated to the university; the gymnasium had the necessary equipment used in the study. The exercises were systematically shown by a physiotherapist and repeated under his/her guideline.

2.3 | Outcome measures

The Haemophilia Joint Health Score (HJHS) version 2.1[12] and the 2-dimensional video-based gait kinematic analysis (2D-GKA)[13] were used as the primary outcome measures. The 6-min walking test (6MWT)[14] and the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-Qol)[15] were used as the secondary outcome measures. The patients were assessed at baseline, following the exercise program, and at the end of the 6-month follow-up period by a researcher physiotherapist experienced in the treatment of PwH.

The HJHS version 2.1, is calculated by adding the global gait score to the sum of 6 joint totals. The test could yield a minimum score of 0, which indicates healthy joint status, and a maximum score of 124 points (20 points per joint × 6+ 4 points for gait score), which indicates severe arthropathy in multiple joints.[12]

The 2D-GKA is a simple, practical and inexpensive method in which a colour camera and passive markers are used.[13] The 2D-GKA is a

TABLE 1 Properties of the therapeutic exercise program applied in the exercise group

Exercise type	Phase I: weeks 1–4 (Intensity/Time/Repetitions/Sets)	Phase II: weeks 5–8 (Intensity/Time/Repetitions/Sets)
Aerobic	40%-50% of HR_{max}/15 min	60%-70% of HR_{max}/15 min
Proprioception	Balance training on one leg on hard ground. 5 repetitions of 10 s for each repetition and 20 s of rest between repetitions	Balance training on one leg on soft ground (BOSU ball). 5 repetitions of 10 s for each repetitionand20s of rest between repetitions
Strengthening	**Level 1**: 1 set, 10 repetitions	**Level 1**: 1set, 15 repetitions
	Level 2: 2 sets, 10 repetitions	**Level 2**: 2 sets, 15 repetitions
	Level 3: 3 sets, 10 repetitions	**Level 3**: 3 sets, 15 repetitions
	Weight resistance for all levels: Yellow Theraband (2.5 lb)	Weight resistance for all levels: Yellow Theraband (2.5 lb)
Stretching	2 repetitions of 2 min for each repetition and 10 s breaks between repetitions	2 repetitions of 3 min for each repetition and 10 s breaks between repetitions

Abbreviation: HR_{max}, maximal heart rate.

valid method that can be used for gait analysis and is moderately to strongly correlated with 3D gait analysis in the sagittal plane (r = .51-.93).[16] Firstly, the fifth metatarsophalangeal joint, the lateral malleolus, the lateral femoral condyle, and the trochanter major were marked as anatomical landmarks. Thereafter, passive markers were attached with double-sided adhesive tapes on the skin. Video records were then obtained with a high-speed 2D video camera (Hero-3 1920 × 1080 pixels, GoPro, USA). The camera was located on the tripod at a distance of 1.5 m from the patient, 0.86 m above the ground and with its optical axis perpendicular to the patients' sagittal axis.[17] After a patient became familiar with the treadmill; that is, when a patient was able to easily maintain his balance without getting support from the grips of the treadmill, the patient was asked to walk on the treadmill at an imposed speed of 1.55 m/s and video records were collected for the 60s. The 2D records were processed using the Kinovea (version .8.15, Kinovea Open Source Project), which is a free 2D motion analysis used to evaluate GKP.[18] During the phases (midstance, preswing, midswing, and late swing phases) requiring a maximal ROM in the knee and ankle joints,[19,20] kinematic analysis was conducted in the sagittal plane only in the lower limbs with joint(s) with arthropathy. The presence of arthropathy was determined according to clinical and radiological examination findings. A significant limitation of motion and loss of strength, bone changes such as osteoporosis, epiphyseal enlargement, subchondral cysts and narrowing of the joint space were considered arthropathy.[21] Images for the analyses of GKP with Kinovea are presented in Figure 1. The 6MWT was applied in an enclosed and quiet corridor in which the distance between the turning points was 20 m. Each patient was instructed to walk as fast as possible for 6 min without running..[14]

The Haem-A-QoL questionnaire including 10 sections and 46 questions was used to evaluate the changes in the QoL of PwH[15]; low scores indicate high QoL.[22]

2.4 | Statistical analysis

Statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp. Armonk, NY, USA). Visual methods (histograms, probability plots) and Shapiro-Wilks test were performed to test normality of data. Descriptive statistics were expressed as mean and standard deviation (SD) for normally distributed data and categorical variables were expressed as number and percentage (%). Chi-square test and Student's *t*-test were used to compare sociodemographic and clinical data between two study groups at baseline. Change in the assessments was compared with the Student's *t*-test between the groups. A p-value of $< .05$ was considered statistically significant. Effect sizes at a confidence interval (CI) of 95% were calculated for the differences. The repeated measures analysis of variance (ANOVA) was used to determine the differences between the values measured at different time points (t0, t1, and t2) within each group. Mauchly's test of sphericity was used to test the assumption of sphericity for repeated measures ANOVA and ($p > .05$) revealed that the assumption of sphericity was provided. When Mauchly's-sphericity test was significant ($p < .05$), the correction coefficient of the Greenhouse-Geisser was preferred. Bonferroni adjustment was performed as post-hoc multiple comparison test and a p-value of $< .017$ was considered statistically significant.

2.5 | Sample size calculation

Sample size was determined using the G-Power program (Heinrich Heine Universität Düsseldorf, Düsseldorf, Germany). Taking the study conducted by El-Shamy et al.,[23] as the reference, a sample size of eight was determined to be adequate both in the experimental and control groups at least to detect a significant improvement in 6MWT at a power of 80% with an effect size (d) of .83 and a type I error of 5%. Anticipating up to a 25% dropout rate, a total of 20 patients were recruited in the study.

3 | RESULTS

In the present study, 20 of 178 patients met the inclusion criteria. One patient from the exercise group was excluded from the analysis as the patient did not complete the therapeutic exercise program due to a

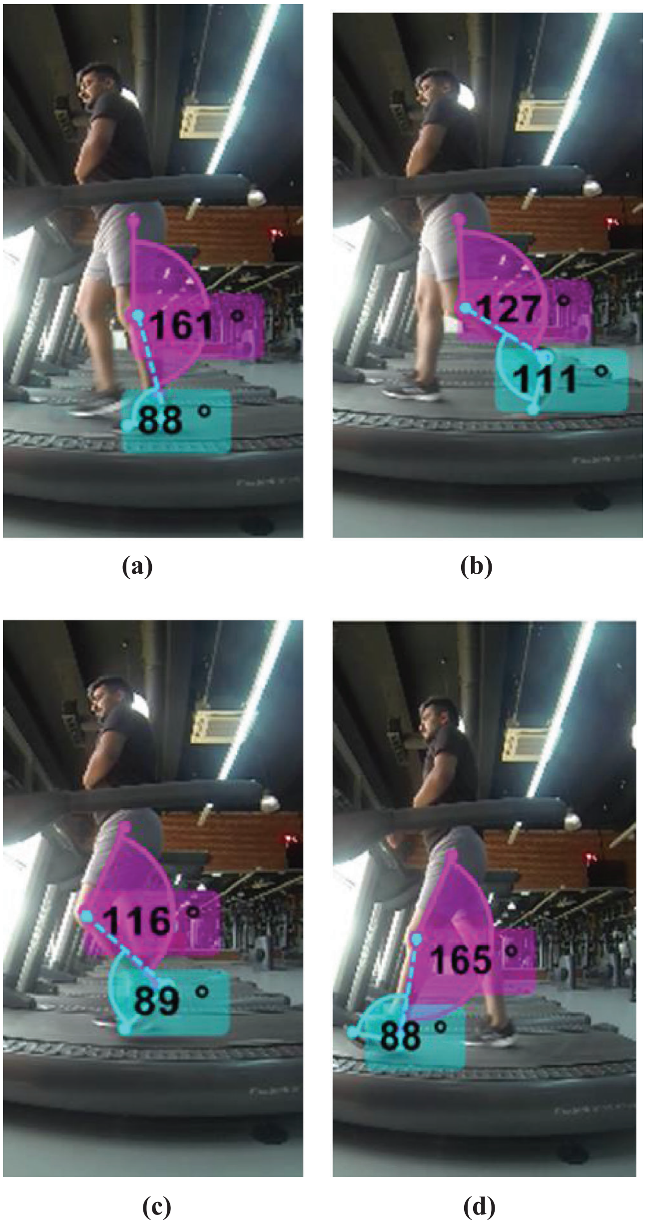

FIGURE 1 Images for the analyses of gait kinematic parameters with Kinovea; **A)** joint angles at the midstance phase; pink angle for knee extension and blue angle for ankle dorsiflexion as calculated by the formula 90-(angle obtained with Kinovea); **B)** joint angles at the preswing phase; pink angle for knee flexion as calculated by the formula 180- (angle obtained with Kinovea) and blue angle for ankle plantar flexion as calculated by the formula angle obtained with Kinovea)-90; **C)** joint angles at the midswing phase; pink angle for knee flexion as calculated by the formula 180-(angle obtained with Kinovea) and blue angle for ankle dorsi flexion as calculated by the formula 90-(angle obtained with Kinovea); **D)** joint angles at the late swing phase; pink angle for knee extension and blue angle for ankle dorsi flexion as calculated by the formula 90-(angle obtained with Kinovea).[18]

lack of interest. The exercise program was extended (15 days) until 19 patients completed 24 sessions. In the 8-week period, the participation rate was 80%. Accordingly, data of 19 PwH, of whom 10 were in the exercise group and 9 were in the control group, were analysed. The patient flow chart is presented in Figure 2.

None of the patients in the exercise group (including those who did not receive prophylaxis) reported joint or muscle bleeding during the exercises and the following day.

3.1 | Sociodemographic and clinical data

The mean age of the patients was 26.3 ± 7.3 years and 26.2 ± 6.8 years in the exercise and control groups, respectively. The mean body mass index (BMI) was 24.4 ± 3.7 kg/m^2 and 23.8 ± 4.3 kg/m^2 in the exercise and control groups, respectively. According to the patient-reported data, all patients were literate and had different educational status. Of the patients, 12 (63.2%) had haemophilia A and 12 (63.2%) had a severe phenotype and were on prophylaxis. Four (21.0%) patients had a history of orthopaedic surgery (knee arthroplasty). Arthropathy was present totally in 35 joints. Arthropathy was present only in the right lower extremity in nine (47.4%) patients, only in the left lower extremity in seven (36.8%) patients, and in both lower extremities in three patients (15.8%).There were no significant differences between the exercise and control groups regarding sociodemographic and clinical data at baseline ($p > .05$ for all; Table 2).

3.2 | Joint health and quality of life

The repeated measures ANOVA revealed that the HJHS-Total score significantly differed between the time points (baseline [t0], after the exercise program [t1] and at the 6th-month follow-up [t2]) in the exercise group ($p < .017$, Table 3). The post-hoc comparative analysis revealed that this difference was due to the improvement after the exercises ($p = .005$). In the control group, no significant difference was determined between the time points regarding any of the HJHS scores and the Haem-A-Qol Total score ($p > .017$ for all; Table 3).

Inter-group comparison of the changes in the HJHS and Haem-A-Qol scores between the baseline and after the exercise program(Δt1-t0) revealed a significant improvement in the HJHS-Total and Haem-A-QoL-Total scores in the exercise group ($p = .003$ and $p = .028$, respectively). However, the comparison of the changes between the baseline and the 6th-month follow-up (Δt2-t0) showed that the recovery obtained by the exercise program in the HJHS-Total and Hem-A-QoL-Total scores was not maintained in the exercise group at the 6th-month follow-up ($p = .283$ and $p = .087$, respectively; Table 4).

3.3 | GKP and functional capacity

The repeated measures ANOVA performed for the t0, t1 and t2 assessments revealed that the values of the knee extension during the

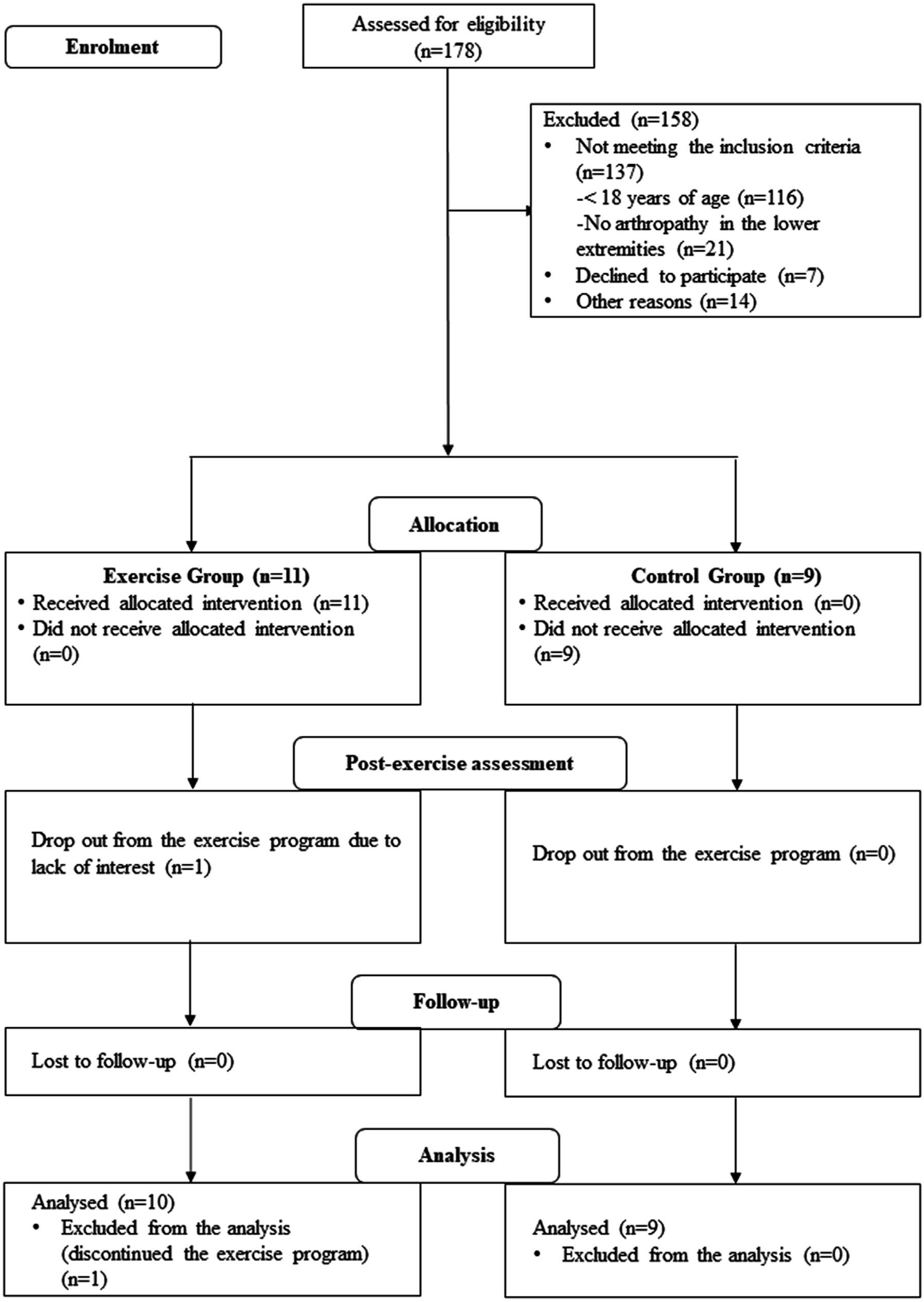

FIGURE 2 Patient flow chart

TABLE 2 Baseline sociodemographic and clinical characteristics of study patients in the whole study group and in the exercise and control groups

	Whole Study Group (n = 19)	Exercise Group (n = 10)	Control Group (n = 9)	p
Age, years	26.3 ± 7.1	26.3 ± 7.3	26.2 ± 6.8	.975
BMI, kg/m^2	24.1 ± 3.9	24.4 ± 3.7	23.8 ± 4.3	.715
Haemophilia Type				
A	12 (63.2)	6 (31.6)	6 (31.6)	
B	7 (37.8)	4 (21.0)	3 (15.8)	.500
Severity				
Severe	12 (63.2)	6 (31.6)	6 (31.6)	.500
Medium	7 (37.8)	4 (21.0)	3 (15.8)	
Treatment regimen				
Prophylaxis	12 (63.2)	5 (26.3)	7 (36.8)	.175
On-demand	7 (37.8)	5 (26.3)	2 (10.6)	
Educational status				
Primary school	0 (.0)	0 (.0)	0 (.0)	.653
High school	11 (57.9)	5 (26.3)	6 (31.6)	
University	8 (42.1)	5 (26.3)	3 (15.8)	
Orthopaedic surgery	4 (21.0)	3 (30.0)	1 (10.0)	.291
Joints with arthropathy	3.5 ± .8	1.9 ± 1.0	1.6 ± .5	
Elbow	9 (47.4)	5 (14.3)	4 (11.5)	.615
Knee	14 (73.7)	8 (22.9)	6 (17.1)	
Ankle	12 (63.2)	6 (17.1)	6 (17.1)	
Affected lower extremity				
Right	9 (47.4)	5 (26.3)	4 (21.0)	.765
Left	7 (36.8)	3 (15.8)	4 (21.0)	
Both	3 (15.8)	2 (10.6)	1 (5.3)	

Data are presented as mean±standard deviation or number (%), where appropriate.
Abbreviations: BMI, Body mass index; SD, Standard deviation.

midstance and late swing phases and the 6MWTvalues significantly differed in the exercise group ($p < .017$; Table 3). The post-hoc comparative analysis revealed that these differences were due to the improvement after the exercises ($p = .009$ and $p = .007$ for knee extension during the midstance and late swing phases, respectively and $p = .001$ for the 6MWT). In the control group, there was no significant difference between the time points regarding any of the GKP and 6MWT values ($p > .017$ for all, Table 3).

Inter-group comparison of the changes in the GKP and 6MWT findings between the baseline and after the exercise program (Δt1-t0) revealed a significant improvement in the exercise group in the knee extension during the midstance ($p = .003$) and late swing phases ($p = .002$), in the ankle dorsiflexion during the midstance phase ($p = .030$), in the ankle plantar flexion ($p = .030$) during the preswing phase, and in the 6MWT value ($p = .001$). However, there was no significant difference in the knee flexion in any of the phases ($p > .05$ for all). The comparison of the changes between the baseline and the 6th-month follow-up (Δt2-t0) revealed that there was a significant difference in the ankle dorsiflexion during the midswing phase ($p = .007$). Furthermore, the improvement that was determined following the exercise program in the 6MWT and in the knee extension during late swing phase were observed to be preserved at the 6th-month follow-up ($p = .013$ and $p = .001$, respectively; Table 4).

4 | DISCUSSION

This study, which investigated the effects of a supervised therapeutic exercise program in haemophiliac adults, demonstrated a significant improvement in the musculoskeletal health, QoL, functional capacity, and GKP in the exercise group as compared with control haemophiliacs.

Treatment approaches in physiotherapy that involve muscle strengthening exercises, joint stabilization exercises, postural exercises, and functional exercises aim at improving joint functions. Previous studies have reported improvement in joint health in PwH

TABLE 3 Intra-group comparisons of the values of primary and secondary outcome measures performed at baseline, after the exercise program, and at the 6th-month follow-up

	Exercise Group Mean±SD				Control Group Mean±SD			
	Baseline (t0)	Post-Exercise (t1)	6 month-follow-up (t2)	*p*	Baseline (t0)	Post-Exercise (t1)	6 month follow-up (t2)	*p*
HJHS								
Ankle (Left + right)	11.9 ± 2.7	9.7 ± 1.2	10.3 ± 2.2	.191	8.0 ± 4.0	8.1 ± 3.6	7.7 ± 3.5	.810
Knee (Left + right)	8.0 ± 5.2	6.3 ± 4.6	7.8 ± 5.1	.018	7.8 ± 6.8	8.0 ± 7.6	8.5 ± 7.1	.130
Elbow (Left + right)	6.50 ± 2.0	6.7 ± 2.6	6.6 ± 1.9	.919	6.7 ± 3.5	7.4 ± 4.2	7.1 ± 3.7	.161
Total	20.3 ± 4.2	16.8 ± 3.7	19.7 ± 3.8	**.005***	15.9 ± 8.9	16.4 ± 9.4	17.3 ± 8.6	.111
6MWT, m	583.5 ± 18.8	629.8 ± 21.3	607.4 ± 21.1	**.001***	544.7 ± 17.7	542.8 ± 20.5	543.3 ± 20.4	.978
GKP, °								
MS Phase								
Knee (E)	172.7 ± 4.6	176.2 ± 3.6	174.2 ± 4.1	**.009***	171.0 ± 7.7	170.3 ± 7.9	170.4 ± 7.4	.561
Ankle (DF)	−2.7 ± 3.2	−.1 ± 3.6	−.9 ± 3.4	.062	2.7 ± 2.5	2.2 ± 3.2	2.2 ± 3.0	.272
PSW Phase								
Knee (F)	43.8 ± 2.9	43.6 ± 4.9	42.8 ± 4.5	.708	42.9 ± 2.4	42.8 ± 3.1	42.8 ± 3.3	.991
Ankle (PF)	12.9 ± 4.3	15.4 ± 3.9	14.6 ± 3.5	.199	14.0 ± 3.5	13.0 ± 3.2	13.8 ± 3.9	.407
MSW Phase								
Knee (F)	55.9 ± 6.1	58.6 ± 4.6	56.8 ± 3.7	.292	59.7 ± 2.5	59.2 ± 3.3	58.4 ± 3.4	.548
Ankle (DF)	−7.6 ± 2.6	−6.3 ± 2.3	−7.2 ± 3.3	.341	−4.5 ± .9	−5.4 ± 2.8	−5.6 ± 2.6	.177
LSW Phase								
Knee (E)	174.9 ± 3.9	178.7 ± 2.4	177.2 ± 4.0	**.007***	170.6 ± 7.9	169.2 ± 6.8	169.0 ± 8.2	.236
Ankle (DF)	−6.1 ± 3.8	−4.7 ± 3.4	−4.2 ± 2.3	.289	−3.2 ± 2.8	−4.5 ± 2.1	−4.6 ± 2.4	.550
Haem-A-Qol (total)	42.9 ± 10.7	39.2 ± 9.7	40.2 ± 10.0	.038	44.2 ± 9.7	44.2 ± 8.4	43.9 ± 8.7	.419

Abbreviations: HJHS, Haemophilia Joint Health Score; 6MWT, 6-minute walking test, GKP, gait kinematic parameters; MS, midstance; PSW, preswing; MSW, midswing; LSW, late swing; Hem-A-Qol, Haemophilia Adult Quality of Life Questionnaire; E, extension; F, flexion; DF, dorsiflexion; PF, plantar flexion; SD, standard deviation.

*Pair-wise comparisons for t0-t1 at a significance level of < .017.

using various exercises.[10,23] Improvement in joint functions was attributed to increased muscle strength and flexibility and decreased oedema.[10] Similarly, in our study, a significant change in HJHS was revealed, by the improvement in muscle strength and ROM parameters due to an 8-week exercise program. However, the assessment performed in the 6th month, revealed that the PwH in the exercise group had worsening in HJHS due to the decrease in muscle strength and joint ROM. The absence of a significant difference between the exercise and control groups at the 6th-month follow-up indicated that the benefits of the exercise program were temporary and thus suggested that PwH should routinely practice their exercise programs. Following the exercise program (at the end of the 8t weeks), the patients were asked to perform the program regularly at home or in the wellness centre (without the supervision of the physiotherapist). Despite this, the participants in the exercise group could not carry out adequate compliance with the program due to a lack of motivation. Thus, the analysis was performed assuming that the participants did not apply the exercises regularly during the period between post-exercise and follow-up assessments. Taking advantage of this experience, we believe that regular follow-up or supervision of PwH by sports or health professionals is required to ensure long-term compliance with therapeutic exercises.

Arthropathy of the joints in the lower extremities causes biomechanical and metabolic changes during gait, which results in a metabolic energy expenditure that is higher than normal.[6] Moreover, deterioration of GKP results in loss of balance and increases the risk of falling in older ages.[25] In the present study, improvements in GKP were observed with the improvements in joint health and neuromuscular coordination via the use of an 8-week therapeutic exercise program. Particularly, an increase was noted in the values of ankle dorsiflexion, plantar flexion, and knee extension which are limited during a gait cycle. The evaluations performed at the 6th-month follow-up revealed a significant difference in some of the GKP (ankle dorsiflexion and knee extension). Although therapeutic exercises did not have a long-term effect on joint health in the present study, the observed prolonged enhancement in the GKP could be explained by motor learning.[26] Motor learning is defined as an array of internal processes associated with practice that will produce changes in how motor activities elicited

TABLE 4 Inter-group comparisons of the changes (Δt1-t0 and Δt2-t0) in the values of primary and secondary outcome measures performed at baseline, after the exercise program, and at the 6th-month follow-up

	Delta (t1-t0)				Delta (t2-t0)			
Scale	Exercise Group	Control Group	p*	Effect Size (95% CI)	Exercise Group	Control Group	p*	Effect Size (95% CI)
HJHS								
Ankle	−2.1 ± 2.6	.1 ± .7	.061	1.2 (−2.2 to .1)	−1.6 ± 2.5	−.3 ± 1.6	.275	.6(−1.6 to .5)
Knee	−1.8 ± 1.8	.3 ± 1.4	**.027**	**-1.2 (−2.2 to −.1)**	−.3 ± 2.1	.8 ± 1.0	.239	.6 (−1.6 to .4)
Elbow	−1.0 ± 2.2	.7 ± 1.0	.086	1.1 (−2.1 to .2)	−.2 ± 2.1	.4 ± 1.0	.520	.4 (−1.5 to .8)
Total	−3.5 ± 3.1	.5 ± 1.8	**.003**	**1.6 (−2.6 to −.5)**	−.6 ± 4.6	1.4 ± 2.5	.283	.5 (−1.3 to .5)
6MWT, (m)	46.3 ± 22.8	−2.4 ± 30.1	**.001**	**1.8 (.7 to 2.8)**	23.9 ± 22.5	−6.9 ± 24.0	**.013**	**1.3 (.3 to 2.8)**
GKP (°)								
MS Phase								
Knee (E)	2.9 ± 2.9	−1.6 ± 2.8	**.003**	**1.3 (.3 to 2.2)**	.3 ± 2.7	−1.5 ± 2.4	.148	.6 (−.4 to 1.5)
Ankle (DF)	2.6 ± 2.9	−.5 ± 1.1	**.030**	**1.3 (.3 to 2.3)**	1.7 ± 2.8	−.5 ± 1.7	.069	.9 (−.1 to 1.8)
PSW Phase								
Knee (F)	−.2 ± 6.1	−.1 ± 2.8	.990	.1 (−.9 to .9)	−1.0 ± 4.8	−.1 ± 4.0	.641	.2 (−1.1 to .7)
Ankle (PF)	2.5 ± 4.0	−1.0 ± 2.0	**.030**	**1.0 (.1 to 2.0)**	1.7 ± 3.6	−.1 ± 2.5	.228	.6 (−.4 to 1.6)
MSW Phase								
Knee (F)	2.7 ± 6.3	−.5 ± 1.7	.147	.7 (−.3 to 1.6)	.9 ± 4.9	−1.3 ± 4.3	.277	.5 (−.5 to 1.4)
Ankle (DF)	1.6 ± 2.5	−.1 ± 1.3	.086	.5 (−.1 to 1.8)	.9 ± 1.4	−1.1 ± 1.4	**.007**	**1.4 (.4 to 2.4)**
LSW Phase								
Knee (E)	3.8 ± 2.8	−.4 ± 2.2	**.002**	**1.6 (.6 to 2.8)**	2.3 ± 2.5	−1.8 ± 1.5	**.001**	**1.9 (.8 to 2.9)**
Ankle (DF)	1.6 ± 4.1	−1.3 ± 3.4	**.153**	.7 (−.2 to 1.7)	2.0 ± 4.1	−1.5 ± 3.6	.059	.9 (−.1 to 1.8)
Hem-A-Qol (total)	−5.1 ± 4.2	.0 ± 4.2	**.028**	**1.2 (−2.1 to −.2)**	−3.1 ± 4.6	.7 ± 4.5	.087	.8 (−1.7 to .1)

Abbreviations: t0, baseline; t1, post-exercise; t2, 6th-month follow-up; HJHS, Haemophilia Joint Health Score; 6MWT, 6-minute walking test, GKP, gait kinematic parameters; MS, midstance; PSW, preswing; MSW, midswing; LSW, late swing; Hem-A-Qol, Haemophilia Adult Quality of Life Questionnaire; E, extension; F, flexion; DF, dorsiflexion; PF, plantar flexion; SD, standard deviation; CI, confidence interval.
*Comparisons were performed using the Student's t-test at a significance level of < .05.

in the context of acquisition of a specific skill.[27] Motor learning becomes permanent when the changes with exercises or activities are repeated frequently in daily life.[28] Given this information, we concluded that the improvement provided by exercises in gait pattern continues for a long time due to frequent repetition of the smooth gait pattern in daily activities. These data suggested that the 8-week therapeutic exercise was effective in improving GKP and maintaining them for a long time.

Since the GKP vary depending on the walking speed,[29] a fixed speed of 1.55 m/s –the average walking speed of adult men[30]- was used for evaluation. Furthermore, during the phases requiring a maximal ROM in the knee and ankle joints (midstance: phase with the most knee extension, preswing: phase with the most plantar flexion, midswing: phase with the most knee flexion, and late swing: phase with the most ankle dorsiflexion), kinematic analysis was conducted.[19,20] It has been supposed that if there is sufficient joint ROM in these phases, the required joint ROM can be achieved in other phases as well. Thus, an analysis was performed in the above-mentioned phases in the present study. To the best of our knowledge, there is no previous study that has demonstrated an improvement in the GKP using a therapeutic approach in PwH. In this regard, the current study contributes to the literature.

The sedentary lifestyle adopted by the PwH due to increased metabolic load associated with the changes in GKP[6] and arthropathy[10] significantly decreases their functional capacity. Mulvany et al.,[10] reported a significant improvement was achieved in functional capacity with a 6-week supervised exercise program in people with bleeding disorders and attributed this finding to the improved cardiopulmonary capacity, vascular circulation, and musculoskeletal system. Similarly, in the current study, the findings of the 6MWT revealed that the functional capacity of our PwH significantly improved. In addition to the factors stated by Mulvany et al.,[10] we also attributed increased functional capacity to the improved GKP. Restriction of joint motion following arthroplasty, arthrodesis or osteoarthritis increases metabolic energy consumption during walking and causes a decrease in functional capacity. Detrembleur et al., reported that improvement in ankle dorsiflexion reduced metabolic load during walking.[31] From this point of view, we think that the improvement in GKP contributes to the recovery of functional capacity in PwH. The metabolic load of walking decreased with improved GKP as demonstrated by the finding that improvement obtained in the GKP and 6MWT value at the end of the exercise program preserved at the end of the 6th-month follow-up.

The QoL of PwH is lower than that of healthy individuals.[22,32,33] Previous studies have reported that physical exercise leads to improvement in QoL in PwH.[9,32] However, in their study in which a specific aquatic exercise program was used, von Mackensen et al.,[33] reported that the exercise provided no significant improvement in the QoL of PwH. In the present study, the patients' QoL improved at the end of the 8-week exercise program. We attributed the improvement in the patients' QoL to the physical recovery and decreased negative mental perceptions such as kinesiophobia.[32] On the other hand, the evaluation of patients at the 6th-month follow-up revealed that patients' QoL would decrease in the time unless the exercises are applied regularly.

The present study has several limitations. Firstly, an optimal randomization was not performed. Secondly, blinding was not implemented in this study. Thirdly, the therapeutic exercise program applied consisted of different types of exercises, which made it impossible to determine exactly which type of exercise resulted in improvement among the PwH. These limitations necessitate randomized controlled trials involving specific types of exercise to support the reliability of the results of the present study.

5 | CONCLUSIONS

This pilot study revealed, an 8-week supervised therapeutic exercise program was successful in achieving improved musculoskeletal health, GKP, functional capacity, and QoL in PwH. Therapeutic exercises provided long-term positive effects on the GKP and functional capacity but did not have a permanent effect on the musculoskeletal health and QoL.

ACKNOWLEDGEMENTS

VD contributed to the design of the study, data collection, data analysis, and writing of the manuscript. NAG contributed to the design of the study and data analysis. SL contributed to data analysis and writing of the manuscript. ABA and HIS contributed to the recruitment of the study subjects and the design of the study. AK, OCB, and OG contributed to the data collection and data analysis. SSK contributed design of the study and data analysis.

CONFICT OF INTEREST

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

DATA AVAILABILITY STATEMENT

The data supporting the findings of the present study are available upon reasonable request.

ORCID

Volkan Deniz https://orcid.org/0000-0003-0779-7721
Sébastien Lobet https://orcid.org/0000-0002-3829-6850

REFERENCES

1. Valentino LA, Hakobyan N, Enockson C, et al. Exploring the biological basis of haemophilic joint disease: experimental studies. *Haemophilia*. 2012;18(3):310–318.
2. Fouasson-Chailloux A, Maugars Y, Vinatier C, et al. Clinical relevance of 3D gait analysis in patients with haemophilia. *Haemophilia*. 2018;24(5):703–710.
3. Suckling LB, Stephensen D, Cramp MC, Mahaffey R, Drechsler WI. Identifying biomechanical gait parameters in adolescent boys with haemophilia using principal component analysis. *Haemophilia*. 2018;24(1):149–155.
4. Stephensen D, Taylor S, Bladen M, Drechsler WI. Relationship between physical function and biomechanical gait patterns in boys with haemophilia. *Haemophilia*. 2016;22(6):e512–e518.
5. Forneris E, Andreacchio A, Pollio B, et al. Gait analysis in children with haemophilia: first Italian experience at the Turin Haemophilia Centre. *Haemophilia*. 2016;22(3):e184–e191.
6. Lobet S, Hermans C, Bastien GJ, Massaad F, Detrembleur C. Impact of ankle osteoarthritis on the energetics and mechanics of gait: the case of hemophilic arthropathy. *Clin Biomech Bristol Avon*. 2012;27(6):625–631.
7. Lobet S, Detrembleur C, Massaad F, Hermans C. Three-dimensional gait analysis can shed new light on walking in patients with haemophilia. *Sci World J*. 2013;2013:284358.
8. 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):194–199.
9. Cuesta-Barriuso R, Torres-Ortuño A, Nieto-Munuera J, López-Pina JA. Effectiveness of an educational physiotherapy and therapeutic exercise program in adult patients with hemophilia: a randomized controlled trial. *Arch Phys Med Rehabil*. 2017;98(5):841–848.
10. Mulvany R, Zucker-Levin AR, Jeng M, et al. Effects of a 6-week, individualized, supervised exercise program for people with bleeding disorders and hemophilic arthritis. *Phys Ther*. 2010;90(4):509–526.
11. d'Young AI. Domiciliary application of CryoCuff in severe haemophilia: qualitative questionnaire and clinical audit. *Haemophilia*. 2008;14:823–827.
12. Hilliard P, Funk S, Zourikian N, et al. Hemophilia joint health score reliability study. *Haemophilia*. 2006;12(5):518–525.
13. Munro A, Herrington L, Carolan M. Reliability of 2-dimensional video assessment of frontal-plane dynamic knee valgus during common athletic screening tasks. *J Sport Rehabil*. 2012;21(1):7–11.
14. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111–117.
15. von Mackensen S, Gringeri A, Ravera S, the HAEM-A-QoL Group. Validation of the haemophilia-specific quality of life questionnaire for adult patients with haemophilia (Haem-A-QoL). *Haematologica*. 2005;90(Suppl 2):S115–S116.
16. Schurr SA, Marshall AN, Resch JE, Saliba SA. Two-dimensional video analysis is comparable to 3D motion capture in lower extremity movement assessment. *Int J Sports Phys Ther*. 2017;12(2):163–172.
17. Damsted C, Nielsen RO, Larsen LH. Reliability of video-based quantification of the knee- and hip angle at foot strike during running. *Int J Sports Phys Ther*. 2015;10(2):147–154.
18. Fernández-González P, Koutsou A, Cuesta-Gómez A, Carratalá-Tejada M, Miangolarra-Page JC, Molina-Rueda F. Reliability of Kinovea® software and agreement with a three-dimensional motion system for gait analysis in healthy subjects. *Sensors (Basel)*. 2020;20(11):3154.
19. Loudon J, Swift M, Bell S. *The Clinical Orthopedic Assessment Guide*. Champaign: Human Kinetics; 2008:395–408.

20. Shultz SJ, Houglum PA, Perrin DH. *Examination of Musculoskeletal Injuries*. Champaign: Human Kinetics; 2005:55–60.
21. Dunn AL. Pathophysiology, diagnosis and prevention of arthropathy in patients with haemophilia. *Haemophilia*. 2011;17(4):571–578.
22. Rambod M, Sharif F, Molazem Z, Khair K, von Mackensen S. Health-related quality of life and psychological aspects of adults with hemophilia in Iran. *Clin Appl Thromb Hemost*. 2018;24(7):1073–1081.
23. El-Shamy SM, Abdelaal AAM. Efficacy of pulsed high-intensity laser therapy on pain, functional capacity, and gait in children with haemophilic arthropathy. *Disabil Rehabil*. 2018;40(4):462–468.
24. Lobet S, Meité N, Koninckx M-I, et al. Implementation and assessment of a self- and community based rehabilitation programme in patients with haemophilia from Côte d'Ivoire. *Haemophilia*. 2019;25(5):859–866.
25. Judge JO, Davis RB, Ounpuu S. Step length reductions in advanced age: the role of ankle and hip kinetics. *J Gerontol A Biol Sci Med Sci*. 1996;51(6):M303–M312.
26. Brach JS, Lowry K, Perera S, et al. Improving motor control in walking: a randomized clinical trial in older adults with subclinical walking difficulty. *Arch Phys Med Rehabil*. 2015;96(3):388–394.
27. Cano-de-la-Cuerda R, Molero-Sánchez A, Carratalá-Tejada M, et al. Theories and control models and motor learning: clinical applications in neuro-rehabilitation. *Neurologia*. 2015;30(1):32–41.
28. Morris ME, Iansek R, Kirkwood B. A randomized controlled trial of movement strategies compared with exercise for people with Parkinson's disease. *Mov Disord*. 2009;24:64–71.
29. Moissenet F, Leboeuf F, Armand S. Lower limb sagittal gait kinematics can be predicted based on walking speed, gender, age and BMI. *Sci Rep*. 2019;9(1):9510.
30. Samson MM, Crowe A, de Vreede PL, Dessens JA, Duursma SA, Verhaar HJ. Differences in gait parameters at a preferred walking speed in healthy subjects due to age, height and body weight. *Aging (Milano)*. 2001;13(1):16–21.
31. Detrembleur C, Leemrijse T. The effects of total ankle replacement on gait disability: analysis of energetic and mechanical variables. *Gait Posture*. 2009;29(2):270–274. Feb.
32. Deniz V, Guzel NA. Do therapeutic exercises improve kinesophobia and health-related quality of life in adult hemophilia patients? A randomized controlled trial. *Int J Disabil Sports Health Sci*. 2020;3(1):11–19.
33. von Mackensen S, Eifrig B, Zach D, Kalnins J, Wieloch A, Zeller V. The impact of a specific aqua-training for adult haemophilic patients – results of the WATERCISE study (WAT-QoL). *Haemophilia*. 2012;18(5):714–721.

How to cite this article: Deniz V, Guzel NA, Lobet S, et al. Effects of a supervised therapeutic exercise program on musculoskeletal health and gait in patients with haemophilia: A pilot study. *Haemophilia*. 2021;1–10. https://doi.org/10.1111/hae.14444