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Lower physical activity and altered body composition in patients with haemophilia compared with healthy controls

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Abstract

Introduction: Patients with haemophilia (PWH) have traditionally been discouraged from engaging in sports and strenuous exercise activities, due to the perceived risk of bleeding complications. This puts PWH at an increased risk to become overweight or obese. However, the benefits of many forms of physical activity seem to outweigh their risks, although activities with significant trauma risk should be avoided.

Aim: To evaluate physical activity patterns and body composition of adult PWH.

Methods: This cross-sectional study compared data on physical activity from tri-axial accelerometers and body composition of 18 male adult PWH (aged 18–49 years) on prophylactic replacement therapy and without acute joint bleedings to those of 24 healthy age-matched controls, by means of *Mann-Whitney-U-Tests*.

Results: Median moderate-to-vigorous physical activity was significantly (p = .000) lower in PWH (34.6 min/day) than in healthy controls (65.2 min/day). Body mass index was almost similar between PWH and controls (25.1 vs 24.2 kg/m^2, p = .431). Yet, we found a consistent trend towards less desirable outcomes across body composition parameters, such as median body fat rate (23.5 vs 17.0%, p = .055) in PWH, compared with controls.

Conclusion: Although physical activity has been recommended for PWH since the mid-1970s, the physical activity engagement of adult PWH was still severely limited, possibly due to over-cautiousness but presumably also in consequence of chronic pain. Poor physical activity engagement may well be expected to contribute to the increased body fat and decreased leg muscle mass. Consequently, policies should focus on improving the knowledge and motivation of PWH to engage in health-enhancing physical activity.

KEYWORDS
actigraphy, body composition, electric impedance, exercise, haemophilia

1 | INTRODUCTION

Joint disease affects 90% of people with severe haemophilia,[1] with ankles, knees, and elbows being the most frequently affected joints.[2] PWH (patients with haemophilia) have traditionally been discouraged from engaging in sports and strenuous exercise activities, due to the perceived risk of bleedings.[3] This approach has triggered an increased risk of becoming overweight or obese,[4] reduced aerobic fitness,[5,6] and reduced mineral bone density.[7] Vigorous physical activity has been shown to be associated with an elevated risk of bleedings in children and adolescent PWH, although the absolute risk is likely to be small.[8] In terms of exercise, a recent Cochrane review concluded that most exercise interventions in PWH improved at least one of the outcomes including pain, range of motion, strength, and walking tolerance, and that hydrotherapy may be more effective than exercising on land for pain relief in adult PWH.[9] Furthermore, therapeutic exercise programmes improved the subjective perception of PWH and some domains of the disease-specific quality of life.[10,11] Although activities with significant trauma risk should be avoided, the benefits of many forms of physical activity seem to outweigh their risks.[12] Because each PWH is unique, the choice of the most suitable sports or exercise programme for an individual patient should be made collaboratively between patient, physician and physiotherapist, and should take the individual patient's physical status, interests and social requirements into account.[13] Physical activity behaviour of children and adolescent PWH was found to be at least equally active than that of healthy controls.[14,15] In contrast, a study that objectively assessed the physical activity of adult PWH concluded that the movement behaviour of adults with severe haemophilia differs from healthy adults, mainly due to less walking and less running.[16] To our knowledge, no objective measurement of time spent in different intensities of physical activity in adult PWH has been carried out to date. Generally, a minimum of 150 min of moderate or 75 min of vigorous-intensity physical activity (or a combination of both) per week is recommended for adults to improve cardiorespiratory and muscular fitness, bone health and reduce the risk of non-communicable diseases and depression.[17] Such aerobic activity should be performed in bouts of at least 10-min duration.[17] Many countries translated this evidence into national guidelines and policies. Although body fat rate has been recommended to be taken into account for factor VIII dose calculation,[18] little is known about the body composition of adult PWH.

Findings reported in this paper represent a secondary analysis of data recorded as potential confounding variables in the JOSEPHA study (Joint-health Outcome Scoring: Exploration in Patients with Haemophilia in Austria), where outcomes of 3D gait analyses, functional, and haematological assessments were primarily assessed. Physical activity and body composition were recorded for this primary analysis in order to correct the primary effects for these potential confounding variables.[19] This prespecified secondary analysis aimed to evaluate physical activity patterns and body composition of adult PWH, by comparing these outcomes with those of healthy age–matched controls.

2 | MATERIALS AND METHODS

2.1 | Study design, setting and participants

This cross-sectional study collected data on objectively measured physical activity and body composition of male PWH aged between 18 and 49 years and healthy age-matched controls.

The study was registered at ClinicalTrials.gov: NCT03541811. PWH were considered eligible if they were 1) diagnosed with severe or moderate haemophilia A or B, 2) aged between 16 and 49 years, 3) able to walk without assistance, 4) treated with prophylactic factor replacement that had been initiated before the age of 18 years, 5) not treated with immune-tolerance therapy, and 6) not suffering from functional impairments caused by other conditions than haemophilia. PWH were recruited when no joint bleedings had occurred within 30 days prior to the examination. In summary, the test group represents adult PWH with a covered demand for substitution and without acute joint bleedings. Control group participants were considered eligible if they were male, aged between 16 and 49 years, and having a physiological and symmetric gait pattern without using aids or assistance. PWH were recruited by contacting eligible patients and during regular visits to the paediatric and adult haemophilia clinics at the *Medical University of Vienna*, Austria. For recruitment of healthy aged-matched controls, students and staff members of the *FH Campus Wien–University of Applied Sciences* were addressed with the study information via in-house corridor monitors and an email newsletter. Further control group participants were recruited by word-of-mouth advertising and snowballing. Study assessments were performed in the movement laboratory of *FH Campus Wien–University of Applied Sciences*, between July 2018 and July 2019. Participants completed all study-related procedures within one visit, except for wearing an accelerometer device over a period of seven consecutive days. Shopping vouchers of 40€ and individual outcome reports were offered as an allowance for participation. The *Ethics Review Board* of the *Medical University of Vienna* approved the study protocol (EC 1261/2017), and all participants provided written informed consent, prior to the collection of data.

2.2 | Outcome measures

Body height was measured with a stadiometer Seca 213 (Seca Vogel&Halke, Hamburg, Germany) to the nearest 0.5 cm. Body size and body weight were measured without shoes and outerwear. A correction of 1 kg was subtracted for clothing. Bodyweight and body composition were assessed with the stationary medical body composition analyser Seca mBCA 515 (Seca Vogel&Halke, Hamburg, Germany) based on bioelectric impedance. All data were recorded during morning time (between 8 a.m. and 12 a.m.). Participants were asked to empty their bladder ahead of the anthropometric data collections. *Body mass index* (BMI) was calculated as kg/m^2, based on measured body size and weight. Participants were considered overweight, or obese when classified by a BMI

from 25.0 to 29.9, or ≥30.0 kg/m^2, respectively. Body composition, specifically body fat rate [%], body muscle mass [kg], left arm muscle mass [kg], right arm muscle mass [kg], left leg muscle mass [kg] and right leg muscle mass [kg] were measured via the bioelectric impedance analysis. Muscle masses of arms and legs were considered relevant because ankles, knees, and elbows are the most commonly affected joints in PWH.[20] After passing through the site-based examinations, participants were instructed to wear a *wGT3X-BT* tri-axial accelerometer (ActiGraph LLC, Pensacola, FL, USA) permanently over a period of seven consecutive days, except for sleeping and water activities. The device was worn with an elastic band on the subjects' right-sided hip. Data were processed with the software *ActiLife version 6.13* (ActiGraph LLC, Pensacola, FL, USA). The widely applied cut-offs of at least 10 hours daily wear-time and a minimum of three valid weekdays and one valid weekend day [21] were applied for data cleaning. Count sampling epoch was set at one minute. The so-called *Freedson Adult VM2 Cut-Offs* were applied to categorise physical activity intensities, where *moderate* ranges from 3.00 to 5.99, *vigorous* from 6.00 to 8.99 and *very vigorous* is above 8.99 metabolic units.[22] The *Freedson VM3 Combination* [22] was applied for the estimation of activity energy expenditure. Daily step counts were recorded, and physical activity bouts were processed as activities of at least moderate intensity, with a duration of at least ten minutes. Two physiotherapists performed the *Haemophilia Joint Health Score* (HJHS) 2.1 on all subjects. The physical examination assessment tool HJHS focuses on three joints most commonly affected in PWH: the elbows, knees, and ankles. It assesses pain, range of motion, and strength, as well as the functional tasks of walking, single-leg jumps, stair ascent, and descent. Outcome measures were transformed into score points according to the summary score sheet [23] provided online by the *International Prophylaxis Study Group* (IPSG), a nonprofit collaborative group of healthcare professionals involved with the assessment and care for PWH. A higher HJHS indicates more impairments. Annualised joint bleeding rates were derived retrospectively from the frequency of joint bleedings, recorded within the past year prior to the examination date. For this purpose, participants were asked to bring their personal documentation booklet.

2.3 | Statistical methods

Normality of data was tested by *Shapiro-Wilk* tests and additional graphical inspections of quantile-quantile plots. Descriptive outcomes were indicated descriptively as means with their corresponding standard deviation (SD), or medians with corresponding interquartile ranges (IQR). IQRs were displayed as lower and upper bounds, that is the 25th and the 75th percentile, respectively. To obtain CI 95% for the difference of medians, *Mood's Median-Tests* were performed with Minitab (Minitab LLC, Munich, Germany). Differences between PWH and the control group were tested with *Mann-Whitney-U-Tests*. Effect sizes *r* were calculated from the test statistic *z* (*z*/sqrt (*n*)). Effect sizes were interpreted as small when $r \geq .1$, medium when $r \geq .3$, and large when $r \geq .5$.[24] Associations between the HJHS and the physical activity parameters were assessed by Spearman's Rho. The targeted sample size of 24 PWH and 24 healthy controls was based on sample size calculation for the aforementioned primary study.[19] Differences in body composition between PWH and controls were additionally analysed in the subgroup of participants, who compliantly wore the accelerometer device for tracking physical activity. Characteristics of participants who were excluded from the actigraphy analysis were compared with those who were included, and possible implications of observed differences on outcome parameters were discussed. Statistical analysis was performed with *SPSS Version 26* (IBM Corp., Armonk, NY, United States). Alpha was set at .05. Exact two-sided *p*-values are reported. Based on Bonferroni correction for 27 statistical tests performed in this analysis, a *p*-value <.002 is considered statistically significant. The reporting of findings followed the *STROBE* checklist for cross-sectional studies.[25]

3 | RESULTS

3.1 | Participants

We recruited 18 adult patients into the PWH group and 24 adult subjects into the control group. Ages ranged from 18 to 49 years in PWH and 20–48 years in the control group. Albeit considered eligible when not treated with immune-tolerance therapy, no PWH with inhibitor history participated in this study. For PWH, we did not reach the intended number of patients due to exhausted capacities of subjects willing to participate. Regarding accelerometer data, five PWH and seven control group participants were excluded in the course of the wear-time validation that assessed whether the accelerometer device had been carried adequately (see methods section on physical activity assessment). Consequently, accelerometer data of 30 participants, thereof 13 PWH, was analysed. Characteristics of the participants analysed for physical activity, and body composition, respectively, are summarised in Table 1.

3.2 | Physical activity

PWH were on average below the widespread recommendation of 10.000 steps that has been suggested to classify individuals as active.[26] PWH were markedly less active across moderate-to-vigorous-physical activity intensities and spent less time in activity bouts, than healthy controls. Median vigorous physical activity was in PWH almost zero (Table 2). Total moderate-to-vigorous physical activity ranged from 11 to 63 minutes per day in PWH and in healthy controls from 31 to 106 min per day. An exploratory analysis showed inverse correlations of the HJHS with physical activity parameters, such as vigorous activity (*Rho* = −.56, $p = .048$, $n = 13$) and activity bouts (*Rho* = −.46, $p = .110$, $n = 13$).

TABLE 1 Participant characteristics of patients with haemophilia (PWH), healthy controls, and participants not assessed for actigraphy

	PWH analysed BIA[a] (*n* = 18)	Controls analysed BIA[a] (*n* = 24)	PWH analysed actigraphy[b] (*n* = 13)	Controls analysed actigraphy[b] (*n* = 17)	PWH excluded from actigraphy[b] (*n* = 5)	Controls excluded from actigraphy[b] (*n* = 7)
Age [years], mean (SD)	29.5 (9.2)	29.2 (8.2)	31.6 (9.8)	30.7 (8.8)	24.0 (4.6)	25.6 (5.9)
HJHS[c], mean (SD)	18.8 (12.0)	2.6 (1.3)	21.5 (12.6)	2.5 (1.2)	11.6 (6.7)	2.7 (1.6)
ABR[d], mean (SD)	4.8 (5.8)	–	3.1 (2.6)	–	9.4 (9.3)	–
Zero joint bleeds, *n* (%)	2 (11.1%)	–	2 (15.4%)	–	0 (0%)	–

[a]Bioelectric impedance analysis (body composition).
[b]Accelerometer-based physical activity assessment.
[c]Haemophilia Joint-Health Score 2.1.
[d]Annualised joint bleeding rate.

3.3 | Body composition

Despite a just slightly higher BMI, PWH had a noticeably higher body fat rate and less muscle mass, with leg muscle mass being more affected than body and arm muscle mass. Median BMI of PWH was 25.1 kg/m^2, and median body fat rate was 23.5% (Table 3). Five (28%) PWH were overweight, and another four (22%) PWH were obese. A secondary analysis showed that PWH who indicated ankle(s) and/or knee(s) affected as target joint(s) (*n* = 14), had even less mean leg muscle mass, when compared with the complete group of PWH (*n* = 18): left leg 5.96 (SD: 0.75) vs 6.06 (SD: 0.77) kg, right leg 5.82 (SD: 0.82) vs 5.96 (SD: 0.84) kg.

Furthermore, we analysed differences in body composition between PWH and controls in the subgroup of participants who compliantly wore the accelerometer device for tracking physical activity. PWH who were assessed for both actigraphy and body composition (*n* = 13) were somewhat older and had a higher HJHS when compared with the complete sample of PWH, including those who were not assessed for actigraphy (*n* = 18; Table 1). Trends for differences in muscle masses observed in the complete sample showed larger effect sizes in this subgroup (Table S1).

4 | DISCUSSION

Some previous studies have reported on objectively assessed physical activity behaviour of children and adolescents with haemophilia. Buxbaum et al. found slightly higher physical activity levels in PWH when compared with healthy controls.[14] This study analysed data of 17 PWH, aged 11–18 years, with severe, moderate, or mild factor VIII or factor IX deficiency.[14] Walker et al. found levels of sedentary time in children (aged 6–18 years, *n* = 65) with chronic diseases, including haemophilia, to be similar to those of healthy peers.[15] While beneficial effects of exercise interventions in adult PWH have been shown in several studies and were summarised in a Cochrane review,[9] little is known about the physical activity engagement of adult PWH. In line with the only objective physical activity assessment on adult PWH,[16] we found adults with severe haemophilia to be less physically active than healthy controls. This observation applies for both, moderate and vigorous physical activity intensities, as well as activity spent in bouts. Median bouts of PWH (at least 10 min duration) accounted for about 35 min of moderate physical activity per week, which is markedly below the recommended 150 min.[17] An international expert panel concluded that all PWH should have the opportunity to take part in tailored and individualised high-quality exercise programmes.[27] Moreover, prescription of physical activity was suggested, as a next step going beyond advice.[28] Several exercise programmes were developed to suit the needs of PHW.[29,30] Our exploratory analysis showed inverse correlations of the HJHS with physical activity parameters. To our knowledge, the association between the HJHS and objectively measured physical activity has not been assessed before in adult PWH. Versloot et al. found

TABLE 2 Accelerometer derived physical activity parameters of patients with haemophilia (PWH) and healthy controls

	PWH (*n* = 13)	Controls (*n* = 17)			
	Median (IQR)	Median (IQR)	Diff. medians (CI 95%)	Effect size *r*[a]	*p*-value[a]
Steps [x/day]	8064 (4968, 14328)	13536 (10512, 16920)	−5472 (−11232, 576)	**.47**	.000
Activity energy expenditure [kcal/day]	334 (206, 446)	643 (482, 881)	−310 (−511, −110)	**.68**	.000
Moderate activity [min/day]	26.0 (14.5, 48.1)	53.8 (45.8, 72.9)	−27.8 (−44.2, −2.5)	**.58**	.001
Vigorous activity[b] [min/day]	0.3 (0.2, 2.1)	6.6 (1.4, 8.6)	−6.3 (−7.7, −0.7)	**.58**	.001
Very vigorous activity[b] [min/day]	0.0 (0.0, 0.0)	0.1 (0.0, 3.6)	−0.1 (−0.3, 0.0)	**.38**	.065
Moderate-to-vigorous activity[b] [min/day]	34.6 (16.0, 52.0)	65.2 (46.9, 81.9)	−30.6 (−65.3, −2.7)	**.62**	.000
Activity spent in bouts[c] [min/day]	4.8 (0.0, 11.2)	11.0 (3.5, 19.6)	−6.2 (−15.4, 4.5)	**.32**	.079

Based on Bonferroni correction for 27 statistical tests performed in this analysis, a *p*-value <.002 is considered statistically significant.

[a]2-sided *p*-values derived from Mann-Whitney-U-Tests with effect size *r* (z/sqrt (*n*), where **bold figures** indicate at least medium-sized effects (*r* ≥ .3).[24]

[b]Physical activity intensities categorised with Freedson Adult VM2 Cut-Offs.[22]

[c]Activities of at least moderate intensity with a duration of at least 10 min.

TABLE 3 Body composition of patients with haemophilia (PWH) and healthy controls

	PWH (*n* = 18)	Controls (*n* = 24)			
	Median (IQR)	Median (IQR)	Diff. medians (CI 95%)	Effect size *r*[a]	*p*-value[a]
Body mass index [kg/m^2]	25.12 (21.55, 29.23)	24.18 (22.59, 25.41)	0.93 (−2.79, 5.32)	.12	.431
Body fat [kg]	18.2 (9.0, 28.0)	13.3 (7.9, 19.2)	4.9 (−1.9, 13.0)	.23	.140
Body fat [%]	23.5 (14.7, 32.3)	17.0 (11.4, 22.2)	6.6 (−3.2, 16.2)	**.30**	.055
Fat mass index [kg/m^2]	6.0 (3.0, 9.6)	4.1 (2.5, 5.6)	1.9 (−1.3, 5.4)	.27	.082
Body muscle mass [kg]	29.51 (28.25, 32.06)	31.92 (28.89, 35.31)	−2.41 (−5.47, 0.81)	.26	.089
Left arm muscle mass [kg]	1.84 (1.69, 2.13)	2.13 (1.81, 2.27)	−0.30 (−0.44, 0.02)	.29	.058
Right arm muscle mass [kg]	1.92 (1.77, 2.11)	2.19 (1.85, 2.26)	−0.27 (−0.42, 0.01)	.28	.071
Left leg muscle mass [kg]	6.09 (5.62, 6.51)	6.44 (5.95, 7.39)	−0.35 (−1.48, 0.27)	**.30**	.053
Right leg muscle mass [kg]	6.08 (5.43, 6.31)	6.53 (6.06, 7.57)	−0.45 (−1.79, 0.12)	**.37**	.016

Based on Bonferroni correction for 27 statistical tests performed in this analysis, a *p*-value <.002 is considered statistically significant.

[a]2-sided *p*-values derived from Mann-Whitney-U-Tests with effect size *r* (z/sqrt (*n*), where **bold figures** indicate at least medium-sized effects (*r* ≥ .3).[24]

negative correlations between the HJHS and self-reported *number of sports activities* (*Rho* = −0.46, *p* < .01) and self-reported *number of sports activities per week* (*Rho* = −0.36, *p* < .05) in Dutch PWH aged 30 to 40 years.[31]

Wong et al. concluded that rates of overweight and obesity vary across the globe, but that of PWH appear to be similar to that of the general population.[32] In agreement with this conclusion, our study observed the BMI of PWH to be similar to that of healthy controls. Moreover, observed rates of overweight and obesity were in PWH (50,0%) similar to that of the general population of Austrian male adults (50,6%).[33] However, the median body fat rate of PWH (23.5%) was noticeably higher than that of healthy controls (17.0%). Henrard et al. reported a similar mean body fat rate of 22.5% (CI 95% 19.4, 24.6) in a sample of 46 adult Belgians with mild, moderate, or severe haemophilia.[18] Albeit with our sample not statistically significant, a consistent direction towards worse outcomes was observed across all body composition parameters in PWH, when compared with healthy controls. In the subgroup of participants who compliantly wore the accelerometer device, the differences concerning muscle masses (between PWH and healthy controls) presented with larger effect sizes. PWH who were assessed for both actigraphy and body composition (*n* = 13) were somewhat older, had a higher (i.e. worse) HJHS, and presumably, were less physically active, when compared with the complete sample of PWH.

4.1 | Strengths and limitations of the study

Strengths of our cross-sectional analysis are that it used objective instruments to measure physical activity behaviour and body composition of adult PWH. The study provides comparisons with age-matched healthy control persons. Limitations of the study are that

due to the voluntary participation in investigations outside routine visits, the sample of PWH is likely not fully representative. Moreover, the samples of both groups were rather small, and a proportion of participants needed to be excluded from the actigraphy analysis due to invalid wear-time data. These facts introduce some risk of bias and limit the generalisability of study findings. Despite dropouts due to invalid wear-time data, most effects related to physical activity outcomes reached statistical significance. Concerning body composition outcomes, where smaller effects were observed, the present analysis is underpowered.

5 | CONCLUSION

Although physical activity has been recommended for PWH since the mid-1970s, the physical activity engagement in this sample of Austrian adult PWH was still significantly reduced, possibly due to over-cautiousness. Albeit not assessed in this study, we assume that physical activity engagement may also be limited by chronic pain. Adult PWH on prophylactic treatment with factor concentrates were found to be physically less active than healthy age-matched controls. The inactivity of adult PWH may well be expected to contribute to their body composition pattern, with increased body fat and decreased leg muscle mass.

Policies should focus on improving the knowledge and motivation of PWH to engage in health-enhancing physical activity. Recommendations and information material could build on the general recommendations published by the WHO and national adaptations thereof.

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CONFLICT OF INTEREST

The authors declare not to have any financial or academic conflict of interest. The manuscript underwent a courtesy review procedure by Takeda, as a general procedure for studies receiving funding via an Investigator-Initiated Research Grant from Takeda.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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