Joint Health, Functional Ability and Physical Activity in Haemophilia

Gewrichtsstatus, Functionele Mogelijkheden en Fysieke Activiteit
bij Patiënten met Hemofilie

door

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Chapter 1

Introduction

Haemophilia

Haemophilia is an X-linked inherited recessive bleeding disorder that is characterized by a deficiency of clotting factor VIII (classic haemophilia, or haemophilia A) or IX (haemophilia B). Haemophilia has a frequency of 1 in 5.000 male births, whereas haemophilia B has a frequency of 1 in 30.000 male births [1]. The level of clotting factor grades the severity of the disease. Patients with severe haemophilia have <1% clotting factor activity, moderate affected patients 1-5% and mild patients 6-40% [2]. Lower levels of clotting factor, especially in the severe patients result in spontaneous haemorrhages in muscles and joints, but may affect other organs as well. Especially repetitive haemorrhages in joints ultimately result in crippling haemophilic arthropathy [3]. Patients with moderate haemophilia may bleed into muscles and joints after minor injuries and mild haemophilia do not bleed spontaneously, but only after medical surgery, dental extractions, or accidents [2].

With the development of cryoprecipitate in 1965 [4], correction of the clotting factor deficit became possible. In the 1980s plasma derived clotting factor concentrates have become available, and recombinant concentrates in the 1990s. Although these new techniques have minimised the risk of blood-transmitted infections such as Hepatitis C and HIV, the cost of concentrates has risen enormously. This has increased the need for careful assessment of treatment results. At first haemophilia was treated with intravenous administration of the missing clotting factor at the occurrence of bleeding only. In the 1960s, professor Inga Marie Nilsson [5] from Sweden started regular prophylactic replacement therapy to prevent bleeding, followed by Professor Van Creveld in the early 1970s [6] and others throughout Europe. In developed countries, early prophylactic treatment has become the standard of care for patients with severe haemophilia. This results in a significant reduction of the development of secondary arthropathy. Decades of clinical experience and numerous retrospective and, recently, prospective studies clearly demonstrate that prophylactic treatment is superior to on-demand treatment, regardless whether the outcome is the number of joint- or life-threatening bleeds, arthropathy evaluated by X-ray or MRI, or quality of life [7-9].

Although the treatment of haemophilia has improved dramatically, especially with the introduction of prophylaxis, still many patients around the world are very much affected by the disease. One reason for this is that a large majority (approximately 80%) of the patients live in developing countries where

financial constraints limit the use of factor concentrates [10]. Another reason is the formation of inhibitory antibodies (inhibitors) to factor concentrates in about 30% of young patients with haemophilia A and in 1-6% of patients with haemophilia B [11]. When inhibitors are present, the treatment is less effective and patients may be more affected by haemophilia in terms of joint status and quality of life [12]. Thus, despite improved treatment strategies, still many patients with haemophilia experience the serious consequences of this disease.

Evaluation of functional health status in haemophilia

Evaluation of joint health in haemophilia has long been performed by using a system based on consensus and developed by the World Federation of Haemophilia (WFH) in the early 1980s [13]. The WFH scoring system assesses aspects of joint health including bleeding frequency, pain, and physical and radiological evaluation (Pettersson score) [13]. This WFH evaluation is still used to assess individual patients and for research purposes, both in developed [14,15] and developing countries [16]. The WFH system, however, has two main shortcomings: lack of psychometric properties (reliability, validity and sensitivity to change have never been established) and its focus on pathology (bleeding frequency) and on body functions and structures (radiological and physical evaluation, and pain). The WFH evaluation does not assess activities, participation or contextual factors. Body functions and structures reflect the function of organs and organ systems; they do not necessarily predict the perception of a person's functioning in daily life [17,18]. Healthcare workers are not just dealing with pathologies and their implications for the body, but with the impact of these conditions on the person. This is particularly the case with a disabling condition such as haemophilia [19].

The introduction of the International Classification of Functioning and disability (ICF; Figure 1) by the World Health Organization has enabled a more comprehensive evaluation of the functional health status. The model includes the aspects of body functions and structures, activities and participation as well as environmental and personal factors [20]. During the past decade the ICF model has been adopted widely and has become the preferred model for describing functional health status in patients [21]. Its adoption in haemophilia has been urged by De Kleijn et al. [19] and has led to the development of several haemophilia specific instruments for different levels/categories of the ICF. For example, on the level of body functions and structures new tools have been developed to detect early changes in joint structure such as Magnetic Resonance Imaging (e.g. [22,23]) and the Haemophilia Joint Health Score (HJHS; [24,25]). On the level of activities both

a performance based (Functional Independence Score in Haemophilia; FISH, [26,27]) and a self-reported outcome measure (Haemophilia Activities List; HAL; [28,29]) have been developed. Both self-report and performance based measures have showed to be necessary because of a low to moderate correlation between these two and the need to report the efficiency and efficacy of physical activity interventions [30,31]. For quality of life, as a summary measure, the disease-specific Hemofilia-QoL [32] was developed for adults, and for children the CHOKLAT and the Haemo-QoL [33,34]. A self-reported measure for functional ability or activity level (according to the ICF) in children is lacking.

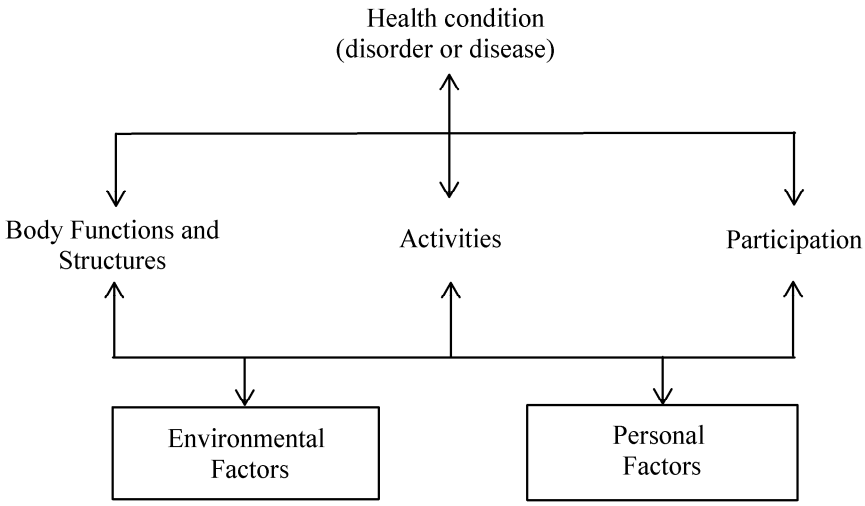

Figure 1: Interactions between the components of the ICF

Physical activity and haemophilia

An active lifestyle has numerous health benefits, especially for primary and secondary prevention of chronic diseases (e.g., cardiovascular disease, diabetes, cancer, hypertension, obesity, depression and osteoporosis) and premature death [35]. For patients with haemophilia physical activity even may have additional benefits for musculoskeletal health including an increase in range of motion of the joints [36], reduction of the number of joint bleeds [37] and improvement of muscle strength and proprioception [38]. Especially in areas where the supply of factor concentrates is inadequate exercise interventions are generally considered important, potentially effective and inexpensive options to treat patients with haemophilia [39-42]. The need for a physical active lifestyle in patients with

haemophilia is further highlighted by the finding that bone mineral density in children with severe haemophilia (FVIII/IX < 1%) is lower than in normal subjects [43] and physical activity has shown to counteract this in healthy subjects [35]. Besides physical benefits, a physically active lifestyle may also contribute to mental health [44]. We underline the importance of psychosocial aspects in patients with haemophilia, but to be able to have a more focussed approach this thesis mainly deals with aspects of physical functioning.

Currently a positive trend is observed in which children with haemophilia are increasingly encouraged to participate in physical activities and sports [45,46]. For example a survey in Dutch adults with haemophilia showed that of those that are on prophylactic treatment a higher proportion than in the general population was active in swimming and cycling [47]. In addition, it was noted that the attitude towards sports among patients with haemophilia has improved, and that the range of practiced sports has increased, most likely due to improved medical treatment [45]. Despite the increased participation in sports, aerobic fitness of children with haemophilia is still reduced compared to healthy peers [48], although it has greatly improved when compared with the study of Koch et al. [49] that dates from 1986.

A recent study shows that engaging in vigorous activity increased the number of bleeds of a trauma, while it did not increase the total number of bleeds [50]. More data are needed to determine the level of risk that is imposed on children engaging in vigorous physical activity such as sports. Also the protective effects of exercise are becoming clearer. For example, exercise could increase muscles strength, which consequently could protect patients from bleeding episodes [37]. Furthermore acute bouts of exercise have shown to increase levels of clotting factor in moderately affected patients [51]. Although promising, these last two studies included small samples and warrant further research.

Aims and outline of this thesis

It is clear that in haemophilia outcome measurement has long been strongly focused on the level of body functions and structures and that functional outcome and physical activity have been underrepresented. This results in little knowledge about the functional consequences that haemophilia has in patients, both with or without prophylaxis. This may be partly explained by a lack of disease specific outcome measures that enable quantification of the limitation with regard to performing functional activities.

The historic cautious attitude of health providers with regard to physical activity may have led to a lack of knowledge in this area. With modern treatment

participation rate and levels of physical activity are changing and may positively affect joint health and physical fitness; however it is not clear to what extent. Furthermore, physical activity is increasingly advocated for haemophilic patients both in developed and developing countries without attempts have been made to systematically review and appraise the available literature on the effects of this paradigm change. Also the acute effects of exercise on clotting factor levels in patients with haemophilia are unclear.

Therefore, the aims of this thesis are:

To study the relationship between joint health and functional ability in patients on intensive factor replacement therapy (chapter 2).

To develop and test an instrument to assess functional health status in children with haemophilia (chapters 3&4).

To quantify habitual physical activity, including type and intensity, in children and adolescents with haemophilia and its relationship with joint health and physical fitness (chapter 5).

To study the current state of knowledge regarding exercise interventions in patients with haemophilia (chapter 6).

To study the acute effects of vigorous physical activity on clotting factor levels in patients with mild and moderate haemophilia A (chapter 7).

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Chapter 2

Joint health and functional ability in children with haemophilia who receive intensive replacement therapy

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SUMMARY

Joint physical examination is an important outcome in haemophilia; however its relationship with functional ability is not well established in children with intensive replacement therapy.

Boys aged 4-16 years were recruited from two European and three North American treatment centres. Joint physical structure and function was measured with the Haemophilia Joint Health Score (HJHS) while functional ability was measured with the revised Childhood Health Assessment Questionnaire (CHAQ38). Two haemophilia-specific domains were created by selecting items of the CHAQ38 that cover haemophilia-specific problems. Associations between CHAQ, HJHS, cumulative number of haemarthroses and age were assessed.

226 subjects – mean 10.8 years old (SD 3.8) – participated; the majority (68%) had severe haemophilia. Most severe patients (91%) were on prophylactic treatment. Lifetime number of haemarthroses (median=5; IQR=1-12) and total HJHS scores (median=5; IQR=1-12) correlated strongly (rho=0.51). Total HJHS scores did not correlate with age and only weakly (rho=-0.19) with functional ability scores (median=0; IQR=-0.06-0). Overall, haemarthroses were reported most frequently in the ankles. Detailed analysis of ankle joint health scores revealed moderate associations (rho=0.3-0.5) of strength, gait and atrophy with lower extremity tasks (e.g. stair climbing).

In this population, HJHS scores summating 6 joints did not perform as well as individual joint scores, however certain elements of ankle impairment, specifically muscle strength, atrophy and gait associated significantly with functional loss in lower extremity activities. Mild abnormalities in ankle assessment by HJHS may lead to functional loss. Therefore, ankle joints may warrant special attention in the follow up of these children.

INTRODUCTION

Currently there is growing interest in objective measurement of health outcome in haemophilia patients. To address this need, outcome measures to measure all levels of the International Classification of Function, Disability and Health (ICF) model of the World Health Organization (WHO) are being constructed. These outcome measures include, among others, the Haemophilia Joint Health Score (HJHS) for the level of body functions and structures [1] and the (Paediatric) Haemophilia Activities List for the level of activities [2-4]. In addition, the Canadian Haemophilia Outcomes-Kids' Life Assessment Tool (CHO-KLAT) and the Haemo-Qol have been developed to measure health-related Quality of life [5,6] .

The relationship between the different ICF domains is an interesting and relevant area of research. Specifically, it is unknown to what extent changes in joint health assessed by a physical examination result in patient relevant changes: i.e. functional limitations and subsequent decrements in social participation and quality of life. Some studies have shown the impact of joint arthropathy on functional ability in adults [7] and children treated on demand [8]; however no extensive research has been performed in a large group of children and teenagers on prophylactic treatment.

In a recent study of a new physical joint examination tool, the Haemophilia Joint Health Score (HJHS), total scores of joint health , comprising the scores of six index joints, including both ankles, knees and elbows, showed no association with a gross measure of functional ability as scored on the revised Childhood Health Assessment Questionnaire (CHAQ) [9]. One possible reason for this could be that there are numerous items on the CHAQ not relevant to the general haemophilia population, especially those who are on prophylactic treatment. Another reason could be that including scores of all joints into the calculation of a score could have a diluting effect by masking important findings of more severely affected individual joints. This is also true for certain items within a joint score, such as crepitus that presumably has small impact on function.

Therefore, we performed an analysis of the relationship between physical/structural joint health (HJHS), life-time number of haemarthroses and functional ability (CHAQ) at the level of the individual joint in comparison to global joint scores. Our main hypothesis was that a higher lifetime number of haemarthroses would lead to worse joint health scores, and consequently would be accompanied by limitations in functional ability on haemophilia-relevant tasks, particularly for lower extremity joints (knees and ankles).

MATERIALS AND METHODS

This study is based on data that was collected for the validation study of the Haemophilia Joint Health Score [9]. Data were collected in 2006 and 2007 from children attending five haemophilia treatment centres in Europe (Stockholm, and Utrecht), United States (Denver) and Canada (Toronto, Montréal) in a collaborative effort of the International Prophylaxis Study Group (IPSG) Physiotherapy Expert Working Group. The validation study was approved by the research ethics boards at all participating centres with written informed consent from all participants or their parents.

Subjects

Boys, aged 4 to 16 years, with all severities of haemophilia A or B, and on all types of treatment (i.e. prophylaxis or on-demand), were enrolled in this study. Primary and secondary prophylaxis, consensus definitions were followed to define the types of treatment used [10]. Excluded were those with an acute bleed within two weeks prior to testing, those with an uncontrolled high titre inhibitor where physical joint assessment would convey an unjustified risk of provoking bleeding, and those with significant concomitant disease affecting joint status and function.

Estimated lifetime number of haemarthroses

Estimations of lifetime number of haemarthroses into each ankle, knee and elbow joint were provided by parents and patients by review of infusion logs, as well as by recall.

Joint physical examination: The Haemophilia Joint Health Score

A physical examination of the six index joints (elbows, knees and ankles) was quantified by the Haemophilia Joint Health Score (HJHS; version 1.0) developed by the IPSG [11]. The HJHS was designed as a more sensitive version of the orthopaedic joint score by Gilbert [12]. It consists of eleven items for each of six joints (swelling, swelling duration, muscle atrophy, axial alignment, crepitus, flexion loss, extension loss, instability, pain, strength and gait) and global gait. The scores for each of the six joints are summed and, together with a score for global gait, the resulting score ranges from 0 to 148 with a score of zero representing best possible joint health. All items are scored using an ordinal categorical scale. Examinations as well as scoring were performed by experienced paediatric physiotherapists trained in using the HJHS.

Functional ability: revised Childhood Health Assessment Questionnaire (CHAQ)

Functional ability was measured with the revised CHAQ [13]. The questionnaire was originally designed for children with juvenile arthritis [14] but has also been applied to other musculoskeletal conditions such as haemophilia [15]. The revised CHAQ consists of 38 questions ($CHAQ_{38}$) describing the ability to perform activities of daily living in eight domains that are likely to be affected by joint limitations (e.g. dressing and grooming and performing activities). The score of the $CHAQ_{38}$ ranges from -2 to 2 asking if each activity in question can be performed 'much worse' (-2), 'a little worse' (-1), 'the same' (0), 'a little better' (1), 'much better' (2) and 'not applicable' in the past week when compared to healthy peers [13]. Because we were only interested in functional limitations, and to prevent positive scores from masking limitations perceived for other items, we recoded positive scores to zero to focus only on functional limitations. This results in a possible scoring range between -2 to 0. The total score on the $CHAQ_{38}$ is the mean score of all items [13].

As the CHAQ was not developed specifically for haemophilia patients, a total score (including e.g. fine motor abilities of the hands) tends to underestimate the severity of haemophilia patients who primarily suffer from elbow, knee and ankle arthropathy. We therefore created two haemophilia specific domains. Items were first selected on face validity (i.e. 'haemophilia appropriate', involving impact on functional ability resulting from joint impairment in elbows, knees and ankle joints). This was completed by authors Van der Net, Groen and Fischer. Subsequently, the scale was reviewed to determine if the selected items indeed had a high percentage of negative scores compared to items that are non-specific for haemophilia.

Item selection for CHAQ haemophilia domains

Two haemophilia-specific domains of the $CHAQ_{38}$ were made: "lower extremities" and "school-/ extracurricular activities". The items of the CHAQ haemophilia domains are listed in Table 1. For the domain "lower extremities" we selected six items of the original $CHAQ_{38}$. For the domain "school and extracurricular activities" the entire domain of the $CHAQ_{38}$ added by Lam et al. [13] was selected. Items 31 ("do climbing activities"), 35 ("keep my balance while playing rough games"), and 37 ("run in a race") were selected for both domains.

Table 1. Item content of two haemophilia specific domains constructed based on a selection from all items of the $CHAQ_{38}$

Lower extremities	**School-/extracurricular activities**
11. climb up five steps	31. do climbing activities
28. ride bike or tricycle	32. play team sports with others in my class
30. run and play	33. play some sports by myself or with a few friends
31. do climbing activities	34. play team sports in competitive leagues
35. keep my balance while playing rough games	35. keep my balance while playing rough games
37. run in a race	36. do activities I usually enjoy for a long time without getting tired out
	37. run in a race
	38. work carefully with my hands

Legend: the numbers before each item refer to the item number of the original $CHAQ_{38}$.

Statistical analysis

Analyses were performed with SPSS version 15.0 for Windows. Descriptive variables are shown as means and standard deviation (for normally distributed data) or as medians, interquartile ranges (IQR; P25-P75) and ranges for data with skewed distributions. CHAQ and HJHS scores were compared by nonparametric tests (Wilcoxon signed rank test) because of skewed distributions. Spearman's correlations were calculated. A correlation of 0.1-0.3 was considered weak, 0.3 – 0.5 moderate and 0.5 -0.7 large [16]. P-values < 0.05 were considered significant.

RESULTS

Subjects

Two-hundred twenty-six boys with haemophilia A or B participated in the study. Their mean age was 10.8 years (range 4-16). Most severe patients were on prophylactic treatment (91%) and 24% had a history of inhibitors. Table 2 shows the demographic characteristics of the study subjects.

Table 2. Demographic characteristics of the subjects

	Severe	Moderate	Mild	Total
Number	153	34	39	226
Mean age years (SD)	10.2 (3.9)	12.0 (3.4)	12.2 (3.0)	10.8 (3.8)
Haemophilia A	134 (88%)	25 (74%)	32 (82%)	191 (85%)
History of inhibitor (≥0.6 Bethesda Units)	37 (24%)	0	0	37 (16%)
Positive inhibitor at the time of study participation	5 (3%)	0	0	5 (2%)
History of prophylaxis	142 (93%)	8 (24%)	1 (3%)	151 (67%)
Current treatment:				
On-demand	14 (9%)	26 (77%)	38 (97%)	78 (35%)
Primary prophylaxis	83 (54%)	2 (6%)	0	85 (38%)
Secondary prophylaxis	56 (37%)	6 (18%)	1 (3%)	63 (28%)

SD, standard deviation or proportion

Descriptive statistics of haemarthroses, HJHS, and CHAQ scores

The median total self-reported lifetime number of haemarthroses (ankles, knees and elbows together) was 5 (IQR=1-12, range 0-150). The total estimated cumulative median number of haemarthroses in the ankles was highest at 2 (IQR= 0-6, range 0-120). Estimated cumulative median numbers of haemarthroses in knees was 1 (IQR= 0-4, range 0-110), and in elbows the median number was 0 (IQR= 0-1, range 0-56). The difference in number of haemarthroses between ankles, knees and elbows were statistically significant ($p<0.01$ for all).

The median total (global 6-joint) HJHS was 5 (IQR= 1-12, range 0-43). The HJHS score for each joint pair was highest for the ankles at 2 (IQR= 0-6, range 0-23), followed by knees at 1 (IQR= 0-3, range 0-14) and elbows with a median score of zero (IQR= 0-1, range 0-18) ($p<0.01$) (Figure 1). The proportions of joints

with zero scores on HJHS for ankles, knees and elbows were 29, 46 and 61% respectively.

The median score of the $CHAQ_{38}$ was zero (IQR -0.06 to 0). The CHAQ haemophilia domains "lower extremities" (median 0; IQR -0.17 to 0) and "school-/extracurricular activities" (median 0; IQR -0.14 to 0) were higher with a broader scoring range which indicates that these haemophilia-specific domains were more sensitive than the overall $CHAQ_{38}$ score ($p<0.01$; Figure 2).

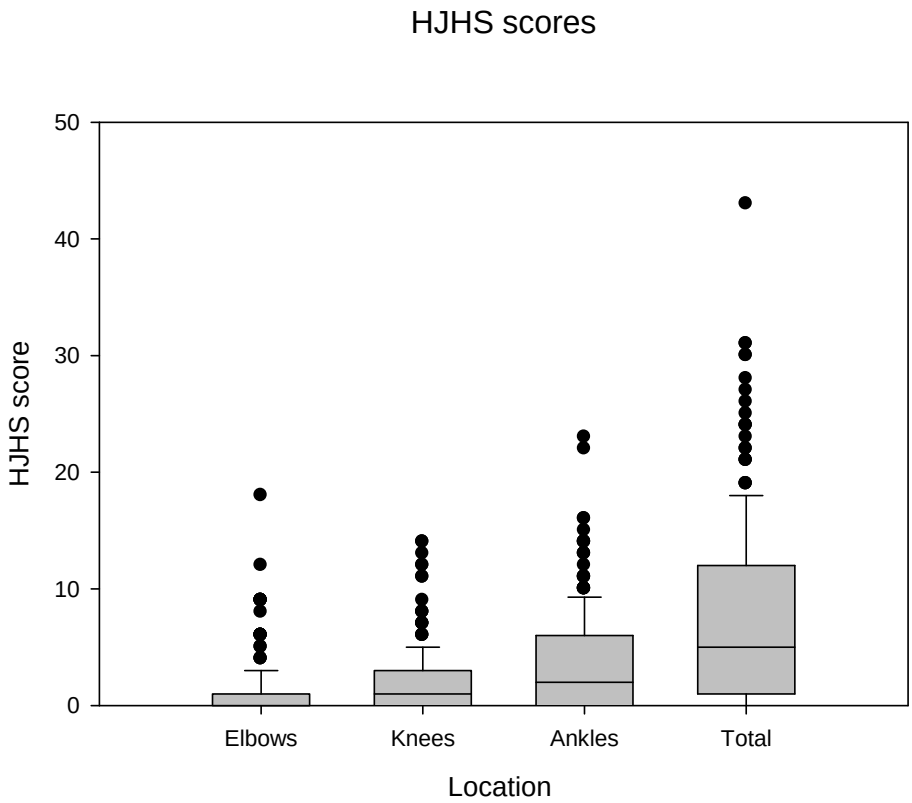

Figure 1. HJHS total score and for the elbows, knees and ankles. The boxes contain all values from the 25th to the 75th percentile (= interquartile range; IQR). The horizontal bar in the middle of the boxes is the median. For the elbows the median is zero and falls together with the 25th percentile. The whiskers represent the 5th and 95th percentile and dots represent outliers.

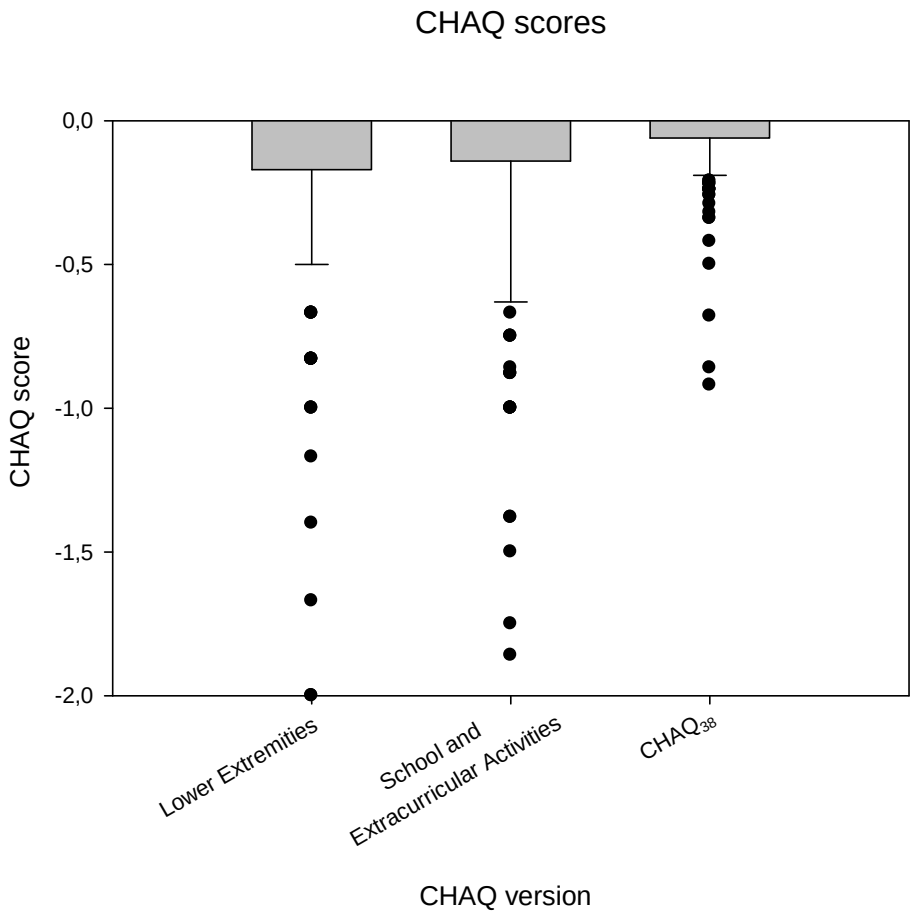

Figure 2. Box-plots of CHAQ score distribution on the two haemophilia specific versions and the $CHAQ_{38}$. A score of zero means best and -2 worst functional ability. The median score for all CHAQ versions is zero. The boxes contain all values from the 25th to the 75th percentile (= interquartile range; IQR). The whiskers in this figure represent the 95th percentile and dots represent outliers.

Association between age, lifetime number of joint haemorrhages and physical joint health (HJHS)

A relatively strong positive association was found between total estimated number of lifetime joint haemorrhages and HJHS total score (rho= 0.51). No correlation was found between age and HJHS total or joint specific scores. In these young boys on intensive treatment, only a weak correlation was found between age and total estimated joint haemorrhages (rho= 0.16). For joint specific scores only the ankles correlated very weakly with age (rho= 0.13).

Relationships among age, lifetime number of joint haemorrhages and functional ability (CHAQ)

The correlations between age, $CHAQ_{38}$ or CHAQ haemophilia domains were weak (rho <0.3, each). Weak correlations were also found between estimated haemarthroses and $CHAQ_{38}$ or haemophilia domains (rho ranging from 0-0.20, each). Number of haemarthroses in the ankles and knees showed very weak associations with $CHAQ_{38}$ or haemophilia domains. Lifetime number of haemarthroses in the elbows correlated weakly with $CHAQ_{38}$ (rho= -0.29) and less with the haemophilia domains lower extremities (rho= -0.20) and school-/extracurricular activities (rho= -0.26).

Relationship between physical joint health (HJHS) and functional ability (CHAQ)

The total HJHS score correlated weakly with the $CHAQ_{38}$ score (rho= -0.19) and even more weakly or not at all with the CHAQ haemophilia domains. Significant associations between the HJHS and CHAQ were found only for the ankle joints (Table 3). No associations with the CHAQ were found for the HJHS scores of elbows and knees. Individual HJHS items on the ankle examination including muscle strength, pain, atrophy and gait correlated consistently with the $CHAQ_{38}$ and haemophilia domains. Muscle strength correlated moderately with the lower extremity domain of the CHAQ (Table 3).

Table 3. Statistically significant associations for ankle Joint Health Scores (HJHS) with the Childhood Health Assessment Questionnaire (CHAQ) ($p<0.05$).

Ankle	$CHAQ_{38}$	CHAQ lower extremities	CHAQ school-/extracurricular activities
HJHS total	-0.23	-0.20	-0.17
HJHS swelling	-0.12		
HJHS swelling duration			
HJHS muscle atrophy	-0.26	-0.17	-0.20
HJHS axial alignment			
HJHS crepitus			
HJHS flexion loss			
HJHS extension loss		-0.11	
HJHS instability			
HJHS pain	-0.16	-0.14	-0.20
HJHS strength	-0.26	**-0.34**	-0.27
HJHS gait	-0.22	-0.29	-0.19

Interpretation: The values shown are spearman correlation coefficients.
The value shown in bold is a moderate correlation. Those that are not bold are weak correlations. Blank cells indicate no significant correlation.

In Table 4 the results of the CHAQ haemophilia-specific domain "lower extremities", according to individual item is shown. Items 11 (climb up five steps), 31 (do climbing activities) and 37 (run in a race) showed moderate associations with aspects of ankle joint health. All three Items correlated moderately with ankle joint strength and items 11 and 31 with ankle joint gait. For atrophy and extension loss of the ankles, consistent but weak correlations were found for all items of this CHAQ domain.

Table 4. Associations HJHS domains for the ankles and CHAQ items for the lower extremities domain ($p<0.05$).

Ankle	Q11	Q28	Q30	Q31	Q35	Q37
HJHS total	-0.26	-0.16	-0.13	-0.17	-0.19	-0.17
HJHS swelling	-0.13				-0.14	
HJHS swelling duration						
HJHS muscle atrophy	-0.27		-0.16	-0.17	-0.29	-0.18
HJHS axial alignment						
HJHS crepitus						-0.12
HJHS flexion loss						
HJHS extension loss	-0.26	-0.17	-0.12	-0.17	-0.16	-0.12
HJHS instability						
HJHS pain	-0.15		-0.11			-0.18
HJHS strength	**-0.39**	-0.28	-0.28	**-0.30**	-0.22	**-0.30**
HJHS gait	**-0.34**	-0.28	-0.19	**-0.31**	-0.15	-0.25

Interpretation: The values shown are spearman correlation coefficients. The values shown in bold are moderate correlations. Those that are not bold are weak correlations. Blank cells indicate no significant correlation. Q11, climb up five steps; Q28, ride bike or tricycle; Q30, run and play; Q31, do climbing activities; Q35, keep my balance while playing rough games; Q37, run in a race.

Table 5 shows the results for the domain "school-/extracurricular activities", by individual item. Items 31 (do climbing activities), 34 (play team sports in competitive leagues) and 37 (run in a race) showed moderate associations with individual items of the ankle examination. All items correlated moderately with ankle joint strength. In addition, item 31 correlated with joint gait. Again, for atrophy and extension loss of the ankles, consistent but weak correlations were found for all items of this CHAQ domain (with the exception of item 38: "work carefully with my hands").

Table 5. Correlations of HJHS domains for the ankles and CHAQ items for school-/extracurricular activities domain ($p<0.05$).

Ankle	**Q31**	**Q32**	**Q33**	**Q34**	**Q35**	**Q36**	**Q37**	**Q38***
HJHS total	-0.17	-0.12		-0.24	-0.19	-0.21	-0.17	
HJHS swelling					-0.14	-0.13		
HJHS swelling duration								
HJHS muscle atrophy	-0.17	-0.13	-0.11	**-0.31**	-0.29	-0.18	-0.18	
HJHS axial alignment								
HJHS crepitus							-0.12	
HJHS flexion loss								
HJHS extension loss	-0.17	-0.18	-0.12	-0.17	-0.16	-0.15	-0.12	
HJHS instability								
HJHS pain				-0.23		-0.17	-0.18	
HJHS strength	**-0.30**	-0.24	-0.17	**-0.36**	-0.22	-0.26	**-0.30**	
HJHS gait	**-0.31**	-0.18	-0.15	-0.20	-0.15	-0.16	-0.25	

Interpretation: The values shown are spearman correlation coefficients. The values shown in bold are moderate correlations. Those that are not bold are weak correlations. *Blank cells indicate no significant correlation. Q31, do climbing activities; Q32, play team sports with others in my class; Q33, play some sports by myself or with a few friends; Q34, play team sports in competitive leagues; Q35, keep my balance while playing rough games; Q36, do activities I usually enjoy for a long time without getting tired out;Q37, run in a race; Q38, work carefully with my hands.

DISCUSSION

This cross-sectional study shows that the study population was relatively unaffected by haemophilia as reflected by a history of only a few haemarthroses and few abnormalities on the HJHS and CHAQ. Lifetime number of haemarthroses correlated strongly with total HJHS scores, but total HJHS scores did not correlate with age and only weakly with functional ability scores. Haemarthroses were reported most frequently in the ankles. Detailed analysis of ankle joint health scores revealed moderate associations of strength, gait and atrophy with lower extremity tasks.

Despite the paucity of abnormalities determined in the study population, the study determined that the ankles were most frequently affected with a median cumulative number of haemarthroses of 2 (IQR= 0-6, range 0-120). Notable is that even with this small number of ankle haemarthroses in young children, key elements of the HJHS physical examination showed moderate correlations with functional tasks. Specifically the HJHS domains of strength, muscle atrophy and gait showed moderate correlation with the calculated CHAQ domains of 'lower extremity activities' and 'school and extra -curricular activities, including ascending stairs, climbing activities, running in a race and participation in competitive team sports. These results show an early limitation of activity and social participation in children with haemophilia secondary to changes in joint health. In addition, the data emphasize the vulnerability of the ankle to haemophilic arthropathy, even in children on primary or secondary prophylaxis. It is possible that the chronic heavy loading of the ankle will demand careful strategies for surveillance and prevention beyond standard factor replacement therapy.

The detection of early ankle dysfunction in the current study may relate to the current method of testing for muscle strength around the ankle. For the HJHS 1.0, 20 heel raises against total body weight has to be lifted to obtain a "normal" score, which is quite demanding compared to the conventional break-method of muscle strength testing that is performed against a manual resistance of a tester [20]. Maybe such a demanding test is required in these relatively unaffected patients in order to detect mild impairment of the ankles. Future studies comparing standard with enhanced testing methods for ankle strength are needed to further inform this question.

The knees and elbows were less frequently affected by arthropathy in this population. Lifetime number of total joint haemorrhages age and total (global 6-joint) HJHS score had poor associations with functional ability (as measured by

$CHAQ_{38}$ score) in this patient sample. The absence of association between joint haemorrhages and functional ability may be a result of the large differences in impact of joint haemorrhages. For example, haemorrhages can differ in factors such as intra-articular blood volume, time lapsed before additional factor replacement, individual (inflammatory) response to blood in the joint and so on. Thus the joint damage that results from haemorrhages can vary greatly. The lack of association between global 6-joint HJHS scores and functional ability could be a result of the masking effect of the summation of individual joint scores, Comparison of individual joint outcomes with global scores must be addressed in future outcome studies of haemophilia prophylaxis.

The absence of associations between overall measures of joint health and functional ability could be attributed to the healthy population (young patients, majority on prophylaxis, low number of joint haemorrhages) and is further amplified by the large number of items of the CHAQ that are not relevant to patients with haemophilia. In addition, as correlations are dependent on the distribution of the data, this study may be disadvantaged by the homogeneity of the data and paucity of abnormalities. The modification of the $CHAQ_{38}$ by defining specific haemophilia-items associations increased sensitivity of the tool, especially for the ankles and especially for those elements that are strongly related to function such as muscle strength. All associations between structural joint health and functional ability were in the direction we expected, that is, better joint health coincided with better functional ability (negative correlations).

Comparison of findings with literature

Ninety-one percent of the young children with severe haemophilia were on prophylaxis, the majority of which was primary prophylaxis. The median number of haemarthroses into individual joints was very low. The study results including minimal joint bleeding, minimal joint damage on physical assessment and minimal disability confirm earlier reports attesting to the efficacy of prophylaxis to prevent joint disease in young children with haemophilia [17-19]. Several studies have reported that ankles were most frequently affected in patients with haemophilia [21-23]. This study shows that even in patients with near optimal joint health, ankles are relatively most affected and relate to lower functional ability in lower extremity tasks. When we compare our results with the literature, it is clear that we were less able to find relationships between joint physical or structural impairment and functional ability. For example, Van Genderen et al. [7] found correlations of 0.69 between radiological (Petterson) score and functional activities (measured by

the HAL) in 34 adult patients (aged 45; SD 14). In another study, Gurcay et al. [8] found a moderate correlation of 0.40 between clinical evaluation score (Gilbert score; [12]) and functional ability measured by the Juvenile Arthritis Functional Assessment Report for children (JAFAR-C) which is a similar measure to the CHAQ in children with haemophilia who were not on prophylaxis therapy. They also found a moderate correlation (r = 0.31) between radiological scores and JAFAR-C. It has to be noted that the children included in the present study are younger, on more aggressive replacement therapy, and with fewer historic haemarthroses compared with subjects in any of the studies described in the cited literature.

Limitations

This study has some limitations. Firstly, data were collected with the aim of validation of the HJHS. The HJHS is intended to be sensitive to early joint impairment. For this study, patients on intensive replacement therapy predominated. This selection of patients most probably leads to an underestimation of the relationship between joint impairment and functional ability in haemophilia. However this analysis gives insight into early manifestations of functional loss in such patients. Secondly, the CHAQ is a measure of functional ability that was not designed specifically for haemophilia. We tried to tackle this by modifying it into two versions that included only haemophilia-specific items. Despite this modification some other important activities might not have been addressed. That is why we emphasize the use of a specific activities list for children with haemophilia in future studies. The paediatric Haemophilia Activities List (PedHAL), which has recently been developed, may be a more appropriate candidate [24]. The PedHAL however was not yet available at the time of this study. Thirdly, the self-reported lifetime number of haemarthroses is a relatively rough measure and may not be reliable. The findings based on this measure should therefore be treated with some caution. We are aware that the results of this study are mainly valid for patients with relatively healthy joint status such as patients on primary prophylaxis.

Clinical implications

From this study we conclude that, in our cohort, subtle changes in joint structure and function are primarily found first in the ankle. Therefore there should be an extra focus on ankle joints in the evaluation / follow up of children with haemophilia who receive intensive replacement therapy. Furthermore, the CHAQ

may not be sensitive enough to pick up early changes in joint impairment in children with haemophilia. This could make the CHAQ less suitable in the early phase of follow up of patients on prophylaxis.

Future directions

Physical and structural joint health is relatively good in children on intensive replacement therapy and mild changes in joint health may not always be detectable by scales of functional activities such as the CHAQ. In future studies, it could be important to incorporate more sophisticated measures, such as gait analysis, that may predict risk for functional impairment. These analyses have demonstrated to some extent the ability to detect sub- clinical changes in gait pattern parameters, which may both reflect subject joint dysfunction and also cause worsening of joint function [25,26]. It may be expected that in the coming decade measures like gait analysis will become of major importance in the detection of early joint impairment for children on intensive treatment and potentially guide early interventions.

Conclusions

This study is a first attempt to describe the impact of early deterioration of joint health on functional ability in children with haemophilia who are treated intensively. The children in this study showed near optimal joint health and functional ability. No clear relationship was found between those two entities, with exception of the ankles. They appear to be the first joints to demonstrate functional loss and therefore may require special attention in the follow up of these children.

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Chapter 3

Development and preliminary testing of a paediatric version of the Haemophilia Activities List (PedHAL)

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SUMMARY

Worldwide, children with hemophilia suffer from limitations in performing activities of daily living. To measure such limitations in adults a disease specific instrument, the Hemophilia Activities List (HAL), was created in 2004. The aim of the present study was to adapt the HAL for children with hemophilia and to assess its psychometric properties.

The structure and the main content were derived from the HAL. Additionally, items of the Childhood Health Assessment Questionnaire and the Activity Scale for Kids were considered for inclusion. This version was evaluated by health professionals (n=6), patients (n=4), and parents (n=3). A pilot test in a sample of 32 Dutch children was performed to assess score distribution, construct validity (Spearman's rho) and reproducibility.

Administration of the PedHAL was feasible for children from the age of 4 years onwards. The PedHAL scores of the Dutch children were in the high end of the scale, reflecting a good functional status. Most subscales showed moderate associations with the joint examination (rho = 0.42 – 0.63) and moderate to good associations with the physical function subscale of the CHQ-50 (rho = 0.48 – 0.78). No significant associations were found for the PedHAL and the subscales mental health and behaviour, except for the subscales leisure & sport and mental health (rho = 0.47). Test-retest agreement was good.

The PedHAL is a promising tool, but further testing in populations with a higher level of disability is warranted to study the full range of its psychometric properties.

INTRODUCTION

Without prophylactic treatment, many children and adults with severe haemophilia suffer from recurrent bleeding episodes of major joints. Eventually these bleeds will result in irreversible joint damage and limitations in activities of daily living. Until now, clinical evaluation of children and adolescents with haemophilia has been limited to measurements on the level of body structures and quality of life [1-3]. In the WHO's International Classification of Functioning, Disability and Health (ICF) [4], activities in daily life are recognized as an important link between structural problems, participation and quality of life. However, currently, no instrument is available to quantify the full range of activities in daily life for children and adolescents with haemophilia.

Recently the Haemophilia Activities List (HAL) has been developed and tested to measure meaningful activities in daily life for adult persons with haemophilia [5,6]. The HAL however, was designed for adults and is therefore not applicable in children. In a recent study on functional outcome, including the HAL, it was stated that "appropriate modifications for the use (of the HAL) in children would be required" [10]. As haemophilia is a life-long condition and symptoms may occur quite early, a paediatric version of the HAL should follow the construct of the HAL, as well as represent the development of daily childhood activities according to age. The PedHAL and the HAL combined will enable continuous monitoring of the activities of daily life from early childhood into late adulthood.

Moreover, the available functional outcome measures for childhood musculoskeletal conditions such as the Childhood Health Assessment Questionnaire (CHAQ) [7] and the Activities Scale for Kids (ASK) [8] are less adequate for the evaluation of our patients. The CHAQ has shown to be a reliable and valid instrument for especially systemic (inflammatory) conditions in the musculoskeletal system (e.g. juvenile idiopathic arthritis or dermatomyositis) [7,9]. The CHAQ therefore lacks a focus on motor tasks that are especially influenced by joints mostly affected in hemophilia (i.e. elbow, knee and ankle joint). The ASK is a generic instrument which focuses on childhood musculoskeletal conditions and has not been validated specifically for children with hemophilia. The ASK is expected to be less valid in a homogeneous population of children with hemophilia since they were only a small group in the validation of the ASK.

This study describes the first steps in developing a disease specific tool that measures (self-) perceived limitation of activities in daily life in children and adolescents with haemophilia based on the construct of the HAL.

MATERIALS AND METHODS

Patients

Patients were recruited from the Van Creveldkliniek in Utrecht, the Netherlands, a supra-regional comprehensive care unit for patients with haemophilia. Patients with mild, moderate and severe haemophilia (A or B) in the age of 4 to 17 were invited to participate. Patients with significant cognitive impairment or insufficient knowledge of the Dutch language were excluded. All children and parents provided a written informed consent and the study was approved by the Institutional Review Board.

Phase I: Item selection

The first version of the PedHAL was developed by selecting and/or modifying items from different sources. Items from Haemophilia Activities List (HAL), the Childhood Health Assessment Questionnaire (CHAQ) and the Activity Scale for Kids (ASK) were considered. Two experts in the field of paediatric disability and haematology were involved in this phase (JN and KF). The aim was to follow the original structure of the HAL, including its seven domains. These domains are 1) sitting, kneeling, standing, 2) functions of the legs, 3) functions of the arms, 4) use of transportation, 5) self care, 6) household tasks, and 7) leisure activities and sports. As a result, relevant items of the CHAQ and ASK were selected in two expert meetings and were categorized into the matching domain of the original HAL. This resulted in version 0.0 of the PedHAL.

Items that were found to be phrased too difficult were corrected to suit the vocabulary of children and adolescents. The process of item selection is visualized in a flowchart in Figure 1.

Phase II: Item evaluation

The PedHAL version 0 was reviewed in two steps: First, health professionals in the field of paediatric haemophilia reviewed the items that were selected and their suggestions were implemented in an adapted version. Secondly, patients and caregivers reviewed the version that resulted from this first step. Reviewing was done in a structured manner: all reviewers were asked to consider the clarity and importance of the individual items. Furthermore, content and style were rated, and general remarks could be added. In addition, to check for potential missing items, children and parents were asked to report important activities that could be negatively affected by haemophilia. These activities had to be ranked from most to least important. Version 0.1 of the PedHAL was created based on the

results of the consecutive reviews and the additions proposed by the children and parents at a debriefing session with the main investigators (WG, JN, KF). Two different versions were made: a child and a parent version.

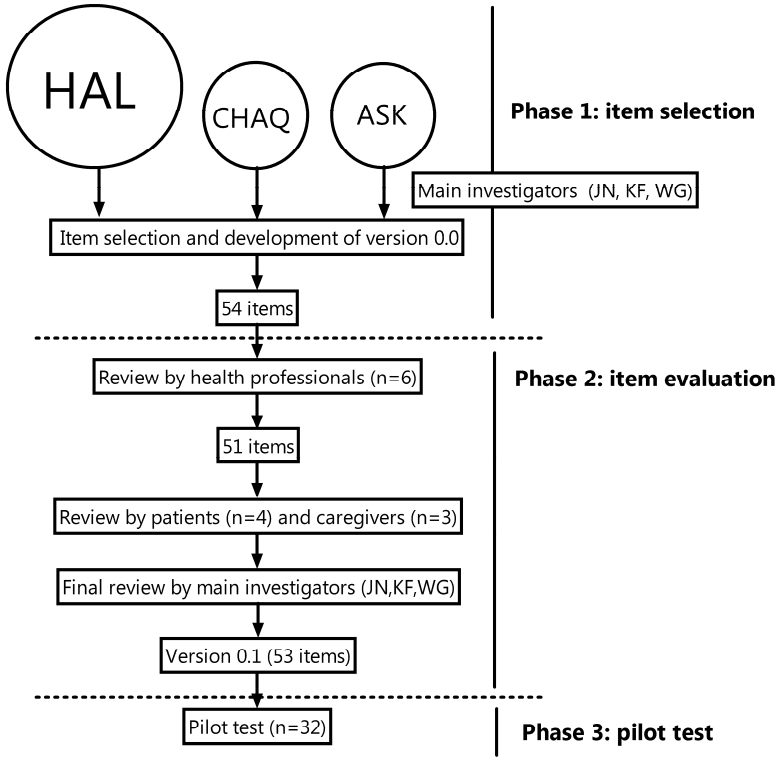

Figure 2. Flowchart of the study. HAL, Haemophilia Activities List; CHAQ, Childhood Health Assessment Questionnaire; ASK, Activity Scale for Kids.

In this study, we administered the parent version for children aged 4 to 7 whereas children of 8 to 18 received the child version. The only difference between the two versions was the use of language in the introduction and in the questions. For children this was: “In the previous month, did you have any difficulty, due to haemophilia, with:”. In the parents version this was: “In the previous month, did your child have any difficulty, due to haemophilia, with:” .

Phase III: Pilot testing

PedHAL version 0.1 was administered to children and parents at the Van Creveldkliniek. For patients 4 to 7 years, one of the parents per child was requested to complete a parent-version. In older patients, both patient and parent completed

the questionnaire. After one to two weeks, the PedHAL version 0.1 was re-administered, to determine reproducibility. Patient-parent concordance was determined for the group of patients of 8-18 years. PedHAL scores were calculated as normalised scores for both scales and a sumscore, according to the method as proposed by Van Genderen [11]. A score of 100 indicates no perceived functional limitation and a score of 0 indicates maximum perceived limitation.

Construct validity was assessed by correlating PedHAL scores to a joint examination for all patients and to three subscales of the Child Health Questionnaire (CHQ-50) in a sub-sample (n=22). The CHQ-50 is a generic health outcome measure for children that comprises of a physical-, behavioural-, and emotional health scale [12,13]. The subscales used for testing construct validity were: physical function (PF), behaviour (BE) and mental health (MH). A joint examination of elbows, knees and ankles was performed by the paediatric haematologist (KF) during routine check-up. Joint health was scored on five aspects: observation of joint swelling, muscular atrophy, joint alignment (varus or valgus position), impaired flexion, and impaired extension. These aspects were scored as a dichotomized score: present (1) or absent (0). These individual sum scores (range 0-28; varus/valgus was not applicable to elbows) were then normalized to a score of 0-100, with 0 indicating bad joint health and 100 indicating optimum joint health. To test for construct validity, the PedHAL scores were correlated to theoretical converging subscale of the CHQ-50: i.e. physical functioning (PF). This subscale contains 6 questions about the (in) ability to perform physical activities. The PF score of the CHQ-50 was expected to correlate moderately to strongly (i.e. 0.4-1) with PedHAL scores. In addition, correlation to two theoretically diverging subscales of the CHQ-50 "behaviour" (BE) and "mental health" (MH) was assessed, expecting no correlation with PedHAL scores.

To determine reproducibility, the PedHAL was sent to all patients and their parents by surface mail one week after their visit to the clinic, requesting to fill out the PedHAL between seven and fourteen days after the first time the PedHAL was completed. The date of completion was documented to determine the exact test-retest interval.

Statistics

Data were analyzed using the statistical package for social sciences (SPSS, version 14). Data were tested for normality and quantitative descriptive statistics (means, standard deviations (SD) and ranges) were used to present domain and sum scores of the PedHAL as well as the joint examination. Reproducibility (test-retest

agreement) and patient-parent agreement were evaluated by Wilcoxon signed rank order test and by calculation of the limits of agreement [14]. The mean difference (systematic bias) ± limits of agreement (random error) contains 95% of the difference in scores of two measurements. Associations between joint health, CHQ-50 and PedHAL scores were analysed using Spearman correlation coefficients. A p-value of <0.05 was considered statistically significant.

RESULTS

Phase I: Item selection

For the item selection procedure a selection of relevant items of the HAL, CHAQ and ASK was made. All 42 items of the HAL, 33 of the CHAQ (nr 1-6, 10-17, 19, 21-38), and 36 of the ASK were considered suitable for the PedHAL. Items of the CHAQ and ASK were categorized into the matching domains of the HAL. It was decided whether the original HAL item was appropriate for children and if the CHAQ or ASK item should be used as a relevant addition to that domain. If necessary, items were slightly rephrased to fit the language ability of children and adolescents (Table 1). This procedure resulted in PedHAL version 0.0. A list of decisions made during this selection procedure can be obtained from the authors.

Table 1. Examples of changes made to original HAL items

Original HAL item	PedHAL alternative
Putting on a tie or closing the top button of a shirt	Fastening a hood or doing up the top button on his/her jacket
Strolling / (window-)shopping	Strolling (e.g. a day at the zoo)
Fine hand movements (e.g. closing buttons)	Fine hand movements (e.g. picking up a Lego, playing computer games)

Phase II: Item evaluation

A first round of item evaluation was done in an expert panel consisting of six health professionals, all working in the field of haemophilia (a physical therapist, a paediatric physical therapist, a paediatric occupational therapist, a paediatrician specialised in haemophilia, a nurse and a physiatrist). They rated most of the items to be clear and appropriate (on a scale from 0-10; 10 being perfect). The content was rated a 6.5 (SD 2.6) and style a 7.2 (SD 0.8). When the majority (i.e. $\geq$3 of 5)

of the health professionals considered an item to be unclear or inappropriate, these items were reconsidered during a debriefing session between the three main investigators. Five items were rated to be unclear and were altered based on the suggestions. One item (sitting on the person carrier on the back of a bicycle) was considered inappropriate and was removed from the list. General remarks concerned the order of the items and redundancy of some items. In addition, some textual amendments were made in order to enhance the clarity of the items.
In the second round of item evaluation, four patients (all had severe hemophilia; mean age 15.8 (SD 1.5) years) and three caregivers (all mothers) reported activities such as walking long distances and participating in competitive sports to be most affected by haemophilia. This was reflected by the importance scores of the individual items. Most activities performed when using the upper extremities (e.g. fine motor tasks) were considered less important, whereas basic activities performed using the lower extremities and more intense ambulatory activities such as walking, running and cycling were considered to be very important. Content was rated at a mean of 7.7±1.3 and style at 8.0±0.7. Based on these results two more items were included, i.e. standing and walking for longer periods of time. All items that were considered unimportant by the majority of patients and caregivers were still retained for the pilot phase after which item reduction could be performed based on a larger sample of negative scores.

Phase III: Pilot testing

Feasibility and Score distribution

A convenience sample of 32 parents (5 fathers and 27 mothers) and 19 children completed the PedHAL version 0.1 at their annual check up at the Van Creveldkliniek. Twenty six patients had haemophilia A and 6 patients had haemophilia B. The mean age of the patients was 8.9 years (SD 3.1, range 4.7 – 17.6). Twenty-four children had severe haemophilia (FVIII/IX < 1%), and 8 had mild haemophilia (FVIII/IX 6-40%). Mean factor activity in the mild patients was 14.4% (SD 5.6). Patients did not differ in age according to severity (severe 9.0 ± 2.7 versus mild 10.8 ± 4.6, p=0.20). All patients with severe haemophilia were treated prophylactically, whereas all patients with mild haemophilia received 'on-demand' treatment. None of the patients had a target joint as defined by three or more bleeds in three months [15].

It took patients and parents approximately 10 minutes to complete the PedHAL and there were no missing values in any of the PedHAL forms. Score characteristics are shown in Table 2. The PedHAL sum scores on the parent forms

ranged from 69 to 100 with a mean score of 95 (SD 9). For the child forms mean scores were 97 (SD 7, range 73 -100) and for the parent forms for children under 8 years old the mean sum score was 93 (SD 11, range 69-100). Noteworthy is the high proportion of activities that were reported to be not applicable (N/A) in the domains of household activities (26 to 59%) and sports and leisure activities (25 to 45 %).The score distribution of subscale and sum scores are visualized by box and whisker plots in Figures 2 and 3.

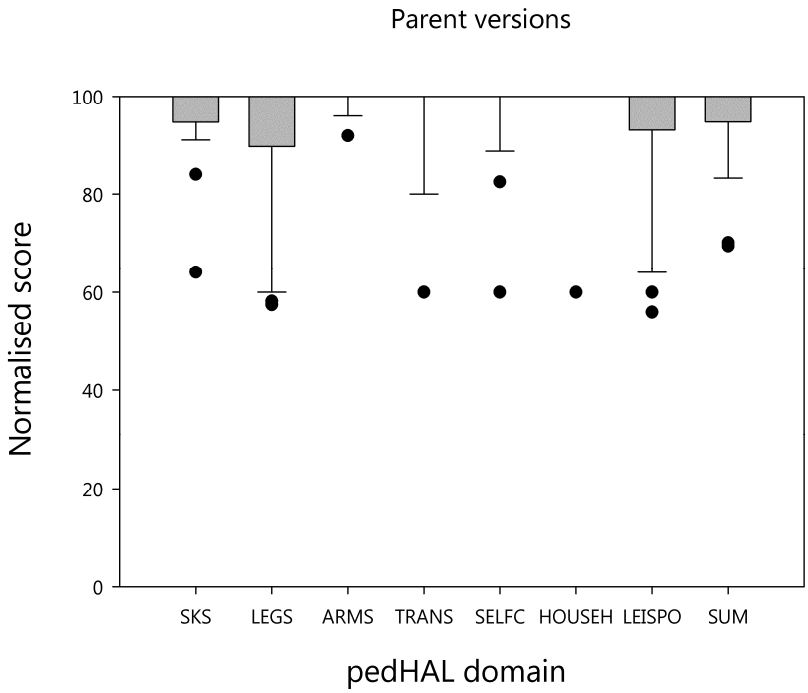

Figure 3. Parents' PedHAL scores according to domains and sum score (n=32). SKS, Sitting kneeling standing; LEGS, functions of the legs, ARMS; functions of the arms; TRANS, use of transportation; SELFC, self-care; HOUSEH, household tasks; Leisure activities and sports; SUM, sum score. Median scores for all domains were 100. Boxes represent 25-50 percentile, whiskers represent 5-25 percentile, dots represent outliers.

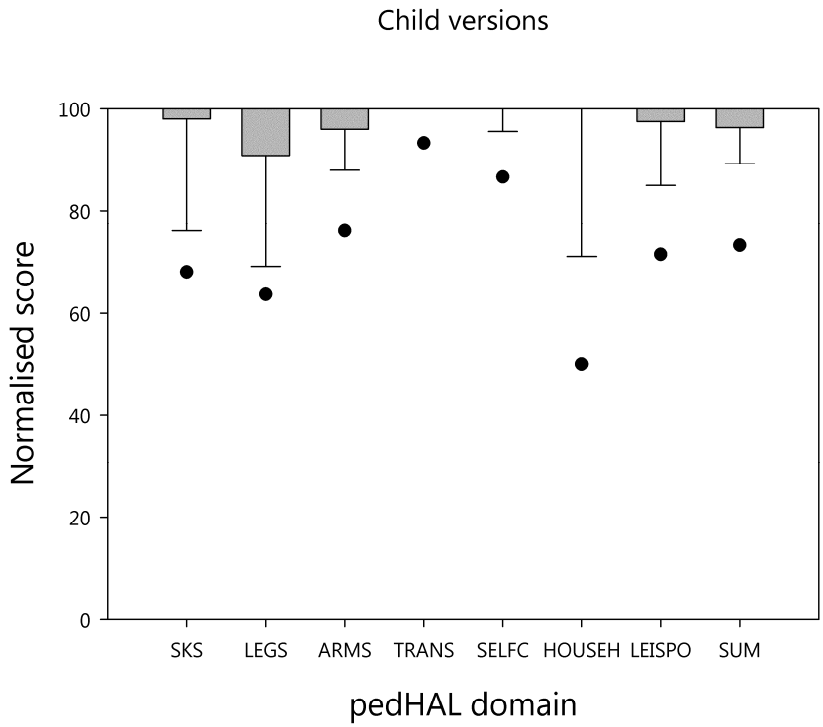

Figure 3. Children's PedHAL scores according to domains and sum score (n=19). SKS, Sitting kneeling standing; LEGS, functions of the legs, ARMS; functions of the arms; TRANS, use of transportation; SELFC, self-care; HOUSEH, household tasks; Leisure activities and sports; SUM, sum score. Median scores for all domains were 100. Boxes represent 25-50 percentile, whiskers represent 5-25 percentile, dots represent outliers.

Table 2. Normalised Score-distribution for the child and parent versions of the PedHAL

				Range			
	Domain	**Mean**	**SD**	**Min**	**Max**	**% Ceiling**	**%Items N/A**
parent forms all 4-18 (n=32)	Sitting kneeling standing	96	9	62	100	70	5
	Functions of the legs	92	15	58	100	67	1
	Functions of the arms	99	2	92	100	88	3
	Use of transportation	97	8	60	100	88	11
	Self care	98	8	60	100	88	4
	Household activities	99	7	60	100	97	34
	Leisure and sport	94	12	56	100	70	34
	Sum score	95	9	69	100	55	12
child forms 8-18 (n=19)	Sitting kneeling standing	96	9	68	100	74	6
	Functions of the legs	94	11	64	100	68	1
	Functions of the arms	97	6	76	100	74	0
	Use of transportation	100	2	93	100	95	14
	Self care	99	3	87	100	84	2
	Household activities	95	13	50	100	81	26
	Leisure and sport	96	8	71	100	63	25
	Sum score	97	7	73	100	53	9
parent forms for children <8 (n=13)	Sitting kneeling standing	94	10	64	100	62	6
	Functions of the legs	87	18	58	100	46	3
	Functions of the arms	100	1	96	100	92	6
	Use of transportation	95	12	60	100	77	21
	Self care	95	12	60	100	77	9
	Household activities	96	13	60	100	90	59
	Leisure and sport	92	15	56	100	62	45
	Sum score	93	11	69	100	38	18

Patient-parent agreement

There were 15 pairs of patient and parent forms available for analysis. As can be appreciated from Table 3, patient and parent forms yielded very similar scores. The Limits of Agreement (LOA) values ranged from 3.4 for the domain "use of transportation", to 28.2 for household tasks. This indicates that there is some disagreement in between patients and their parents especially in the latter domain of household tasks.

Table 3. Patient-parent agreement of the PedHAL (n=15)

	Parent		Child		*p*-Value	LOA
Domain	**mean**	**SD**	**mean**	**SD**	**(Wilcoxon)**	
Sitting kneeling standing	96.4	9.8	95.5	10.0	0.72	-0.5 ± 10.0
Functions of the legs	95.6	9.4	95.0	10.0	0.50	-0.4 ± 7.6
Functions of the arms	98.7	2.9	97.6	6.2	0.52	0.0 ± 10.0
Use of transportation	100.0	0.0	99.6	1.7	0.32	0.7 ± 3.4
Self care	99.3	2.9	98.7	3.5	0.59	-0.5 ± 7.8
Household activities	100.0	0.0	93.6	14.9	0.11	0.7 ± 28.2
Leisure and sport	96.4	6.8	96.0	8.0	0.92	-1.1 ± 10.9
Sum score	97.4	5.3	96.5	7.1	0.40	-0.3 ± 7.1

Interpretation: A p-value >,0.05 as assessed by the Wilcoxon signed rank test means that scores on parent and child versions did not differ statistically.

LOA: Limits Of Agreement. Values represent the change in mean scores (systematic bias) ± the borders of the 95% confidence interval of the change in scores (random error).

Reproducibility

For the test-retest analysis 17 parent forms and 9 child forms were available, corresponding with response rates of 53 and 47% respectively, which was considered to be quite low. The interval between test and retest was 11.3 days (SD 6.3; range 3 - 29). The results of the test retest analysis for parents and children can be appreciated from Table 4. Reproducibility, as assessed by a Wilcoxon signed rank order test, showed no differences on the level of subscales and sum score of the PedHAL on test and retest for both parent and child forms. The limits of agreement were low on most subscales for the parents' and the child forms.

Table 4. Test-retest values for both parent and child versions of the PedHAL (n=17).

		Test		Retest			LOA
	Domain	**mean**	**SD**	**mean**	**SD**	***P***	**LOA**
Child	Sitting kneeling standing	100.0	0.0	99.5	1.5	0.32	-0.5 ± 0.6
(n=9)	Functions of the legs	99.6	1.2	99.2	2.4	0.65	-0.4 ± 1.3
	Functions of the arms	99.1	1.8	99.1	2.7	1.00	0.0 ± 2.0
	Use of transportation	99.3	2.2	100.0	0.0	0.32	0.7 ± 0.6
	Self care	99.8	0.7	99.3	1.6	0.32	-0.5 ± 0.6
	Household activities	96.2	7.6	97.5	7.1	0.79	0.7 ± 1.5
	Leisure and sport	99.8	0.7	98.7	4.0	0.65	-1.1 ± 1.3
	Sum score	99.5	1.0	99.2	2.2	1.00	-0.3 ± 2.0
Parent	Sitting kneeling standing	99.5	2.1	99.9	0.6	0.32	0.4 ± 2.9
(n=17)	Functions of the legs	99.2	1.6	99.5	1.1	0.18	0.2 ± 1.3
	Functions of the arms	100.0	0.0	100.0	0.0	1.00	0.0 ± 0.0
	Use of transportation	100.0	0.0	100.0	0.0	1.00	0.0 ± 0.0
	Self care	100.0	0.0	100.0	0.0	1.00	0.0 ± 0.0
	Household activities	100.0	0.0	100.0	0.0	1.00	0.0 ± 0.0
	Leisure and sport	99.8	0.9	100.0	0.0	0.32	0.2 ± 1.7
	Sum score	99.7	0.7	99.8	0.3	0.10	0.2 ± 0.9

Interpretation: A p-value >,0.05 as assessed by the Wilcoxon signed rank test means that scores on two tests did not differ statistically.

Construct validity

Table 5 shows the results of divergent and convergent validity for PedHAL with subscales of the CHQ-50 and joint examination. Patients of which a CHQ-50 was available for analysis (n=22) were of similar age as the other 10 patients (mean 10.4 versus 9.0 years respectively, p=0.28). Furthermore there was no difference in haemophilia severity between the groups (27.3% and 20% with mild haemophilia respectively, p=0.62). The scores of the domains of the PedHAL correlated significantly with the subscale “physical functioning” of the CHQ-50, ranging from 0.48 (p=0.03) in the domain “functions of the arms” to 0.74 for the domain “self-care” (p<0.01). As expected, scores of the PedHAL subscales showed very low correlation with the CHQ-50 subscales “behaviour” and “mental health”. The only exception was the association between the PedHAL domain “leisure activities and sport” and Mental Health of the CHQ-50 (0.47, p=0.03). In contrast, five PedHAL

domains showed significant and moderate correlations with joint health (0.42 - 0.68). Two PedHAL domains, “functions of the arms” and “self-care”, showed the least correlation with joint health.

Table 5. Correlation of PedHAL domains with CHQ-50 domains and Joint Examination (n=22)

	CHQ *PF*		**CHQ *BE***		**CHQ *MH***		**JE**	
Domain	**rho**	***p***	**rho**	***p***	**rho**	***p***	**rho**	***p***
Sitting kneeling standing	0.59	<0.01	0.19	0.41	0.18	0.45	0.62	0.00
Functions of the legs	0.61	<0.01	0.14	0.56	0.24	0.3	0.59	0.00
Functions of the arms	0.48	0.03	0.18	0.44	0.34	0.13	0.18	0.35
Use of transportation	0.71	<0.01	0.41	0.06	0.29	0.21	0.68	0.00
Self care	0.74	<0.01	0.26	0.25	0.28	0.22	0.36	0.06
Household activities	0.54	0.02	0.19	0.44	0.04	0.86	0.42	0.04
Leisure and sport	0.70	<0.01	0.41	0.06	0.47	0.03	0.63	0.00
Sum score	0.57	0.01	0.14	0.55	0.20	0.39	0.59	0.00

CHQ PF, CHQ subscale physical functioning; CHQ BE, CHQ subscale Behaviour; CHQ MH, CHQ subscale mental health. JE, Joint Examination. Values are Spearman correlations (rho).

DISCUSSION

Our study describes the development of the paediatric version of the HAL. Subsequent testing in a convenience sample of 32 patients showed good construct validity, reproducibility and patient parent agreement. Reliability (discriminative ability) could not be assessed due to homogeneity of the functional status of the study population.

Development

The development of the PedHAL was based on the existing validated construct of the HAL. This enabled the procedure to be less complex than the original steps that were necessary for the development of the HAL. A structured evaluation of both content and style was performed by health care professionals, patients and caregivers. This proved to be a very successful method to transform the HAL into a paediatric version. Moreover, the involvement of the patients and caregivers in the designing process enhanced the degree of face validity of the PedHAL and has been recommended by several authors [14,16]. We are aware of the fact that we might have introduced some redundancy into the PedHAL, especially in the

domain sports and leisure activities. We accepted this in this stage of the development of the PedHAL. In a later stage, when more data are available, item reduction could be considered, making the PedHAL shorter and even more feasible to use.

Score distribution

In general, both PedHAL scale and summary scores were high in this Dutch sample. Due to intensive treatment, these patients were a relatively unaffected patient population in terms of their joint status and consequently in their activities of daily living. Therefore, the ability of the instrument to detect clinically relevant changes and to describe the functional activity level beyond the average in relatively healthy populations could not be assessed. Profound ceiling effects were present in all PedHAL subscales (i.e. >50% of respondents at maximum score). The sum scores of the PedHAL were comparable to those of healthy children as measured with the Activity Scale for Kids (93.1, SD 6.4) [17]. This finding is in accordance with previous reports on Haemophilia Joint Health Score (HJHS) [18], physical fitness [19], and activities [20] in a comparable Dutch patient group. From a clinical perspective, the interpretability of the scores is improved by reporting performance in several subpopulations including the full spectrum of disability. Therefore data of the children with very limited disability are only a first step to fully appreciate the potential of the PedHAL. Testing the PedHAL in patient populations with less favourable joint status is mandatory to fully understand the psychometric properties of the PedHAL 0.1 version that now has been developed.

Reproducibility

Reproducibility can be assessed either by agreement or reliability statistics. We chose limits of agreement (LOA as a measure of agreement, because it is more stable over different population samples than reliability parameters such as the intraclass correlation coefficient (ICC). Agreement statistics are preferable in all situations in which the instrument will be used for evaluation purposes [21].

Despite the advantages of the LOA, values found in this study should be treated with caution due to the small sample size and to the skewed (ceiling effect) distribution of the PedHAL scores [22]. This implies that the LOA values found in this study are most certainly underestimated. Therefore, to really understand the reproducibility of the PedHAL it is of great importance that it is assessed again in a sample of children with a higher level of disability.

Construct validity

We addressed construct validity by correlating PedHAL scores with three subscale scores of the CHQ-50 and to joint health. As expected, significant and moderate to strong associations were found between the PedHAL and the physical function domain of the CHQ-50. In addition, most PedHAL subscales did not correlate with the subscales "behaviour" and "mental health" of the CHQ-50. The only exception to this was the association between the PedHAL domain "leisure activities and sport" of the PedHAL and Mental Health of the CHQ-50. This might be supported by the common notion of 'be active and feel good', which is advocated to promote an active lifestyle. The PedHAL domains "functions of the arms" and "self-care" did not correlate with joint health. This may be explained by the fact that these domains of the PedHAL are related to functions of the upper extremities, which were mostly unaffected in our patient sample. These results combined provide preliminary evidence for the construct validity of the PedHAL.

Clinical implications

Our intention was to keep the original structure of the HAL intact as much as possible, as well as to represent the development of daily childhood activities according to age, this is to enable longitudinal follow up of health outcome in patients with hemophilia from childhood to adulthood. We recognise that this approach resulted in an instrument which could not discriminate in this Dutch sample of children with very mild functional limitations. However, based on the experiences with the performance of the adult version of the HAL, it is expected that in different populations, the PedHAL will be able to discriminate between children with severe, moderate and mild disability. Therefore, the PedHAL is anticipated to become a very valuable addition to the repertoire of outcome measures.

Future research

The current evaluation of the Dutch PedHAL shows a need for additional evaluation of this instrument in children and teenagers with more functional limitations, for example severe haemophilia patients who have not been treated with early prophylaxis. Such studies will enable pooled analyses of item performance, scale validity and calibration of scores in a variety of international populations. In addition, this will provide further insight into the clinical interpretation of PedHAL scores.

In summary, the PedHAL seems feasible for use in children. The scores of the Dutch children were predominantly high, reflecting a good functional status. Results of the pilot test concerning reproducibility and construct validity are encouraging. We conclude the PedHAL to be a promising tool, but further testing in populations with a higher level of disability is warranted to study the full range of its psychometric properties.

ACKNOWLEDGEMENTS

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Chapter 4

Functional Limitations in Romanian children with haemophilia: further testing of psychometric properties of the Paediatric Haemophilia Activities List

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SUMMARY

Children with haemophilia suffer from joint bleeds which eventually result in limitations in performing activities of daily life. Recently the Paediatric Haemophilia Activities List (PedHAL) has been developed and tested in a Dutch cohort of children with intensive replacement therapy. The psychometric properties of the PedHAL in children not receiving intensive replacement therapy are not known. The objective was to gain further insight into the psychometric properties of the PedHAL as well as to assess the functional health status of Romanian children and adolescents with haemophilia.

Children attending to the rehabilitation center of Buzias in Romania were sampled consecutively. Construct validity of the PedHAL was evaluated by concurrent testing with objective and subjective measures of physical function and functional ability. Reproducibility was tested by a 3-day test-retest by intraclass correlation coefficient (ICC) and limits of agreement (LOA). Responsiveness to rehabilitation was assessed by Haemophilia Joint Health Score (HJHS) and PedHAL.

Twenty-nine children with severe (n=25) or moderate (n=4) haemophilia participated. Mean age was 13.2 years (SD 4.0). Median score of the PedHAL was 83.5 (IQR 47.9-90.5). The PedHAL correlated moderately with HJHS (rho=-0.59), FISH (rho=0.65) and CHQ-PF (rho=0.40) and not with CHQ-MH, CHQ-BE and 6MWT. Test retest reliability was good (ICC = 0.95). LOA was 17.4 points for the sum score. HJHS scores improved slightly after rehabilitation, whereas PedHAL scores did not change.

In general, construct validity and test-retest reliability were good, test-retest agreement showed some variability. Therefore, currently the PedHAL may be more appropriate for research purposes than for individual patient monitoring in clinical practice. Romanian children with haemophilia have significant impairments in joint health and functional ability as measured by objective and subjective measure.

INTRODUCTION

Without prophylactic treatment, children and adults with severe haemophilia suffer from recurrent bleeding episodes of major joints. Eventually these bleeds will result in irreversible joint damage, chronic pain, and limitations in activities of daily living. Until now, clinical evaluation of children and adolescents with haemophilia has been limited to measurements on the level of body structures and functions and quality of life [1-3]. In the World Health Organisations' (WHO) International Classification of Functioning, Disability and Health (ICF) [4], activities in daily life are recognized as an important link between structural problems, participation and quality of life. However, until recently, no instruments were available to quantify functional activities in children and adolescents with haemophilia.

Recently the Haemophilia Activities List (HAL) has been developed and tested to measure meaningful activities in daily life for adults with haemophilia [5,6]. The HAL however, was designed for adults and is therefore less suitable to use in children. Moreover, the available functional outcome measures for musculoskeletal conditions such as the Childhood Health Assessment Questionnaire (CHAQ) [7] and the Activities Scale for Kids (ASK) [8] are less adequate for the evaluation of our patients, as haemophilia predominantly affects ankles, knees, and elbows. Therefore, a paediatric version of the HAL (the PedHAL) was created and preliminarily tested in Dutch children with haemophilia [9]. This pilot test of the PedHAL showed that administrating the questionnaire was feasible, but resulted in very high scores, indicating a group of Dutch children treated with early prophylactic treatment [9]. The high scores on the PedHAL obtained in this group hampered the analysis of psychometric properties. Consequently there is a need for additional evaluation in children with more functional limitations. For example in severe haemophilia patients who have not had the privilege to be treated with early prophylaxis, as is the case in Romanian children. In addition, the ability of the PedHAL to detect changes over time is unknown. Insight in the ability to detect changes over time is warranted to substantiate the efficacy and efficiency of treatment of children and teenagers with haemophilia. The aims of the present study were twofold: 1) To study construct validity, reproducibility and responsiveness of the PedHAL. 2) To gain insight into the functional health status of Romanian children with haemophilia, who are not on intensive replacement therapy.

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health status of Romanian children with haemophilia, who are not on intensive replacement therapy.

MATERIALS AND METHODS

Patients

Romanian children with haemophilia A or B, with and without current inhibitors, aged 4 to 18, who are admitted to the Buzias Rehabilitation centre (devoted to treating children with diabetes and haemophilia), were invited to participate. Inclusion criteria were: subjects or parents being able to read and communicate the Romanian language well enough to complete the PedHAL and a signed informed consent form. Excluded were those with no parent or guardian available and those with significant cognitive impairments.

Study procedure

Study procedures are shown in Figure 1. Romanian children and adolescents with haemophilia who attended to the Buzias Rehabilitation centre were asked to participate in the study. On this occasion the Functional Independence Score in Haemophilia (FISH), PedHAL, Child Health Questionnaire 50 (CHQ-50), and a 6 Minute Walking Test (6MWT) test were performed according to available manuals and guidelines. The CHQ-50 and the PedHAL for children under 8 years old were completed by the parent or caregiver. The physical therapists performed their regular treatment (and were asked to log their treatment modalities, e.g. hydrotherapy, and goals, e.g. muscle strength, range of motion etc.). After treatment the physician subjectively rated the health status of the patients as “improved”, “a little better”, “better”, “about the same”, or “worse”, compared to before treatment. Demographic and clinical data, as well as HJHS, FISH, PedHAL and 6MWT were collected within the first (2-3) days after arrival at Buzias. In addition, reproducibility of the PedHAL was assessed after 3 days. After the rehabilitation (duration varied between children) the PedHAL and HJHS were measured.

All measurements were performed by a trained haematologist and physical therapist who attended to a 2 day workshop in fall 2009, which was organized by JN,WG,PH and MS. This workshop consisted of theory sessions, explaining the theoretical background, as well as extensive practical “break-out” sessions to practice the clinical skills for the HJHS and FISH (JN) and 6 minute walk test (6MWT) (WG). All study procedures were approved by the Ethical board of the University Emergency Children Hospital, Louis Turcanu ,Timisoara

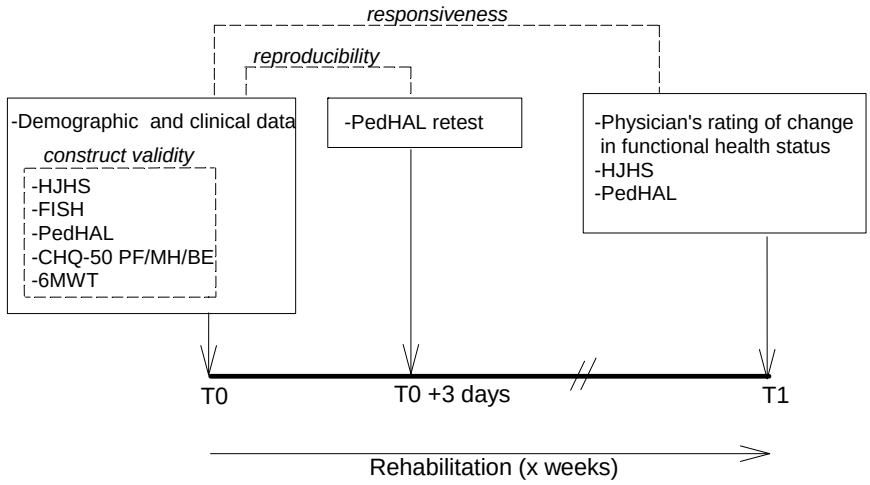

Figure 1. Schematic overview of the study. The outcome measures obtained at different time points during the study are shown in the boxes. The psychometric analyses performed in this study are shown in italics. T0 represents the patient's entry at the Buzias rehabilitation centre. T1 is the discharge from the centre. The length of stay at the rehabilitation centre per varied per patient.

Outcome measures

All documents and tools were translated from English into Romanian language by a professional translator.

Paediatric Haemophilia Activities List (PedHAL version 0.11)

The PedHAL is a measure of self perceived functional limitations. It was developed together with patients, their parents as well as health professionals involved in haemophilia care. It contains 53 items across 7 domains and can be completed by both parents and children themselves (Appendix I). It takes about 10-15 minutes to complete the PedHAL. A raw score is converted to a normalized score that ranges from 0 (worst functional status) to 100 (best possible functional status). Initial testing of this questionnaire showed promising results with regard to feasibility and psychometric properties such as reproducibility and validity [1]. Due to a higher bleeding frequency in patients in countries with minimal available prophylaxis the recall period for the PedHAL has been limited from a month to one week. A bleeding free interval of one week seemed realistic in this population.

Haemophilia Joint Health Score (HJHS) version 2.0

Joint function was measured with the HJHS, an 8-item impairment measure of the six key index joints: knees, elbows and ankles. The 8 items are: duration of

swelling, severity of swelling, muscle Atrophy, crepitus on motion, flexion loss, extension loss, joint pain and muscle strength. The items are scored by grade of severity of impairment. For example: a flexion loss less than 5º scores a zero, whereas more than 20º flexion loss results in a score of 3. Scores are summed up to form joint totals and these are further summed and are supplemented with a score for global gait (i.e. observation of performance of walking, stair climbing, running, and hopping on one leg). Thus a final HJHJS score and ranges from 0 (no impairment) to 124 (maximal impairment for the six main joints). The reliability and validity of the HJHS have been established before [2,3].

Functional Independence Score for Haemophilia (FISH)

The FISH was developed to provide an instrument to assess the functional independence of patients with haemophilia, using an objective, performance-based assessment instrument [4]. The FISH measures the patient's independence in performing activities of daily living (grooming and eating, bathing, dressing), transfers (chair and floor) and mobility (walking and step climbing). Each function is graded from 1 to 4 depending on the amount of assistance the patient needs in performing the function (1: unable to perform; 2: able to perform with assistance/aid; 3: able to perform, but not like other healthy individuals; 4: performs like other individuals). Total score ranges from 0 (functionally fully dependent) to 32 (functionally fully independent). The reliability, validity and responsiveness to change have been established earlier [5].

Six minute walking test (6MWT)

The 6MWT is a valid and reliable measure of functional walking ability [6] and has been used in the evaluation of various clinical populations. The test was performed according to the guidelines of the American Thoracic Society, including standardized encouragements [7]. The 6MWT has shown to be feasible for use in children with chronic conditions affecting the musculoskeletal system, such as haemophilia, juvenile arthritis and spina bifida [8]. The outcome of the six minute walk test is total distance covered in 6 minutes and this was also expressed as percentage of predicted by comparing it to established reference values [9]. In addition, heart rate was measured by a Polar heart rate monitor (Polar F1; Polar Electro, Kempele, Finland). Heart rate in beats per minute (bpm) was obtained immediately before and after the 6MWT. Post exercise heart rates were also expressed as percentage of predicted maximum for age (i.e. 220 - age).

Child Health Questionnaire 50 parent form (CHQ-50)

The CHQ-50 is a generic health outcome measure (questionnaire) for children containing a physical-, behavioural-, and emotional health scale [10,11]. For this study three subscales were used for testing construct validity, specifically, physical function (PF), behaviour (BE) and mental health (MH). Scoring was performed according to the users manual [10], and possible scores range from 0 (worst health) to 100 (best health) for each subscale.

Statistics

Data analysis was performed using SPSS 17.0 (Chicago, Il, USA). Quantitative descriptive statistics were used to present demographic and clinical data of the patients as well as scores of the PedHAL, FISH and 6MWT.

Internal consistency, the extent to which items in a scale are intercorrelated, was determined by Chronbach's alpha. A Cronbach's alpha of 0.70 to 0.95 is proposed to be acceptable [12]. Higher values (>0.95) are indicative of redundancy, whereas lower values (<0.70) indicate lack of correlation.

Construct validity of the PedHAL was assessed by calculating associations between PedHAL and FISH, HJHS and 6MWT variables using Pearson or Spearman correlation coefficients where appropriate. We expected to find at least moderate correlations between the PedHAL on the one hand and HJHS, FISH and CHQ-PF on the other hand. We anticipated finding a low association of the 6MWT with the PedHAL sum score. However, moderate associations were expected to be found between the 6MWT and PedHAL domains that mainly contain items on lower extremity function ("sitting kneeling standing" and "functions of the legs"). Furthermore we expected to find no associations between the PedHAL and the behaviour and mental health scales of the CHQ. Finally, we expected to find lower PedHAL scores than in the Dutch sample we studied earlier [1].

Reproducibility of the PedHAL was assessed by relative agreement (intraclass correlation coefficient; ICC) as well as absolute agreement (Limits of Agreement; LoA) [12]. Relative test-retest reliability of the PedHAL was determined by the intra-class correlation coefficient ($ICC_{2,1}$) using the absolute agreement definition [13]. The 95% confidence intervals for the ICCs were calculated. Values of test-retest reliability of a measurement higher than 0.70 were considered as acceptable reliability [12]. The systematic error (the mean of difference scores of test and retest) was checked by a Wilcoxon signed rank test.

Responsiveness of the PedHAL and HJHS to a physical therapy intervention (i.e. to detect improvements following treatment) was quantified by

the standardized response mean (SRM) and is calculated by dividing the mean change in scores by the standard deviation of these changes [14]. The SRM estimates clinically relevant change in the measure by standardizing relative to the between-patient variability in change scores [15]. SRM values of 0.2, 0.5, and 0.8 represent small, moderate, and large values for responsiveness, respectively [15]. The SRM has been widely used as an index of responsiveness for health status measurement tools, both in haemophilia [5] and other musculoskeletal disorders [16,17]. The significance level was set at 0.05.

RESULTS

Patient characteristics

We studied 29 consecutive patients at the Buzias rehabilitation centre. Ten patients only visited the clinic for a short period, of which 3 patients stayed three days or longer but left the clinic without rehabilitation resulting in twenty-two patients completing baseline assessment and a PedHAL retest. Nineteen patients completed the rehabilitation programme with pre and post measurements. Patient characteristics are shown in Table 1. Twenty-five patients had haemophilia A and 4 patients had haemophilia B. The mean age of the patients was 13.2 years (SD 4.0, range 5.6 – 17.9). Twenty-five children had severe haemophilia (FVIII/IX < 1%), and 4 had moderate haemophilia (FVIII/IX 1-5 %). Age was similar across severity (severe 13.3 ± 4.1 versus moderate 12.7 ± 4.4, p=0.79). All patients were treated on-demand, including three children using home-treatment/home-infusions. Nearly half of the patients had a knee as a target joint, one third had an elbow as target joint, while target joints in ankles were less frequent.

Score distribution and internal consistency

It took patients and parents approximately 10 minutes to complete the PedHAL and there were no missing values in any of the PedHAL forms. Scores of the PedHAL are shown in Table 2. The PedHAL sum scores ranged from 19.2 to 99 with a median score of 83.5 (IQR 47.9-90.5). In the domains ‘Functions of the arms’ and ‘self-care’ respectively 45% and 55% of the respondents scored the best possible score (i.e. the activity that never was a problem). The score distribution of domains and sum scores are visualized by box and whisker plots in Figure 2.

Also noteworthy is the high proportion of activities that were reported to be not applicable (N/A) in the domains of household activities (27 %) and sports and leisure activities (48 %). The internal consistency values (Chronbach’s alpha) of

the domains were high (>0.9) with exception of 'use of transportation' and 'functions of the arms' (0.65 and 0.77 respectively).

Table 1. Patient characteristics and test results (n=29)

Variable	Mean (SD) *	Number (%)
Patient characteristics		
Age (years)	13.2 (4.0)	
Heigth (m)	1.54 (0.18)	
Weigth (kg)	47.0 (17.3)	
Days lost from work/school past 6 months	16.4 (10.3)	
Current inhibitor		3 (10%)
Type and severity		
A, severe		21 (72%)
A, moderate		4 (14%)
B, severe		4 (14%)
Home treatment		3 (10%)
Target joints	1.9 (1.2)	
left ankle		3 (10%)
right ankle		8 (28%)
left knee		13 (45%)
right knee		14 (48%)
left elbow		9 (34%)
right elbow		11 (38%)
Joint bleeds past 6 months (Nr)	3.5 (2.0-6.5)	
Test results		
PedHAL (0-100; 100=best possible score)	83.5 (47.9-90.5)	
HJHS (0-124; best possible score is 0)	11.0 (4.0-23.5)	
FISH (0-32; best possible score 32)	32.0 (25.0-32)	
CHQ-PF (0-100; best possible score is 100)	66.7 (51.4–87.5)	
CHQ-BE (0-100; best possible score is 100)	60.0 (30.0-60.0)	
CHQ-MH (0-100; best possible score is 100)	75.0 (65.0-85.0)	
6MWD (m)	366.2 (83.8)	
6MWD (%predicted for age)	55.3 (26.3)	
Heart rate before 6MWT (beats/minute)	87 (11)	
Heart rate after 6MWT (beats/minute)	112 (15)	
Heart rate after 6MWT (%predicted for age)	54 (7)	

* Joint bleeds, PedHAL, HJHS, FISH and CHQ-PF, CHQ-BE, CHQ-MH are shown as median (IQR).

Table 2. Normalised Score-distribution and internal consistency of the PedHAL

Domain	Median	IQR	Range		% Ceiling	% Items N/A	Crohnbach's alpha
			Min	Max			
Sitting kneeling standing	76.0	32.0-91.0	10.0	100.0	32	5	0.94
Functions of the legs	74.5	42.7-86.1	0	100.0	27	8	0.96
Functions of the arms	86.7	95.0-76.7	15.0	100.0	45	8	0.77
Use of transportation	80.0	43.3-100.0	0	100.0	11	13	0.65
Self care	97.5	72.2-100.0	34.3	100.0	55	3	0.94
Household activities	80.0	65.0-100.0	0	100.0	31	27	0.95
Leisure and sport	65.0	30.2-90.0	0	100.0	17	48	0.96
Sum score	83.5	47.9-90.5	19.2	99.4	34	14	0.98

Construct validity

The PedHAL showed a moderate negative correlation with the HJHS scores (rho=-0.59) and a moderate positive correlation with FISH scores (rho = 0.65).The scores of the PedHAL correlated significantly with the subscale “physical functioning” of the CHQ-50 (rho = 0.40). Scores of the PedHAL domains showed non-significant and low correlation with the CHQ-50 subscales “behaviour” and “mental health” (rho =0.36 and 0.16 respectively). The 6 MWT (as % predicted for age) did not correlate significantly to the PedHAL sum score (rho =0.13). Moreover, no correlations were found between the 6MWT and the domains “sitting kneeling standing and “functions of the legs” (rho=0.12 and 0.09 respectively).

Reproducibility

For the test-retest analysis, 22 forms were available. The interval between test and retest was 3 days in all cases. The results of the test retest analysis for the PedHAL can be appreciated from Table 3. Reproducibility, as assessed by a Wilcoxon signed rank order test, showed no differences on the level of domain and sum score of the PedHAL with exception of “sitting kneeling standing” which was somewhat higher on the retest occasion. ICC’s ranged from 0.68 for “functions of the arms” to 0.99 for “household activities”. The ICC for the sum score was good (0.95). The limits of agreement ranged from 17.5 for “sitting kneeling standing” to 77.7 for “household activities” for the domains and was 17.4 for the sum score.

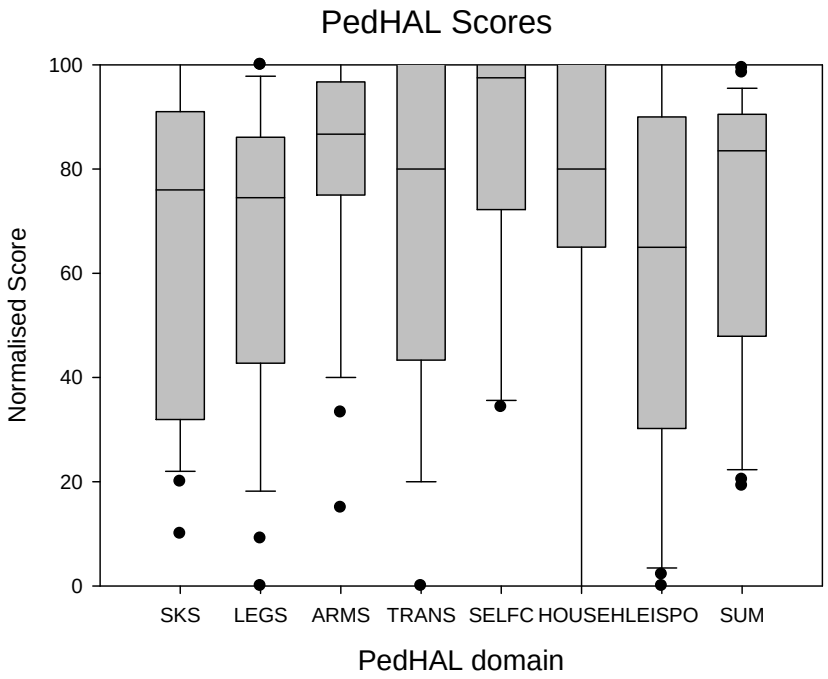

Figure 2. PedHAL scores according to domains and sum score (n=29). SKS, Sitting kneeling standing; LEGS, functions of the legs, ARMS; functions of the arms; TRANS, use of transportation; SELFC, self-care; HOUSEH, household tasks; LEISPO, Leisure activities and sports; SUM, sum score. The horizontal bar in the middle of the boxes is the median. For the elbows the median is zero and falls together with the 25th percentile. The whiskers represent the 5th and 95th percentile and dots represent outliers.

Responsiveness

Nineteen patients followed a conventional short rehabilitation program at Buzias rehabilitation centre. Rehabilitation comprised of a programme with a median duration of 2 weeks (range 1-4). Therapy sessions were performed with a median frequency of 5 times per week (range 5-7) and had a median duration of 120 minutes (range 90-120). Therapy sessions were tailored for each patient and comprised several modes of therapy. Therapy consisted of hydrotherapy (86%), electrical stimulation (33%), ultrasound (14%) and massage (10%). Reported goals of therapy were gaining strength (100%), flexibility (95%) balance (71%) and proprioception (57%). The physician rated health status as being improved in 16/19 patients. Nine patients were rated as “a little better”, 7 as “better”, 1 as “about the same”, and 1 patient was rated as being “worse”, compared to before treatment. For

1 patient this data was missing. Table 4 shows the mean values of PedHAL and HJHS before and after rehabilitation at the Buzias rehabilitation centre in nineteen patients. Median HJHS scores decreased significantly, and there was a SRM of -0.9. The PedHAL pre and post treatment was similar. The mean change in scores was positive (improvement) in four domains of the PedHAL and negative (deterioration) in four domains. The calculated SRM's for the PedHAL were small with the largest values for "sitting kneeling standing".

Table 3. Test-retest results of the PedHAL (n=22)

	Test		Retest				
Domain	**Median**	**IQR**	**Median**	**IQR**	***p*-Value (Wilcoxon)**	**$ICC_{(2,1)}$ (95% CI)**	**LOA**
Sitting kneeling standing	69.8	30.1-90.5	78.0	44.0-94.5	0.01	0.94 (0.81-0.98)	-5.1±17.5
Functions of the legs	74.5	42.3-85.8	77.8	45.7-90.8	0.18	0.92 (0.82-0.97)	-3.2±21.1
Functions of the arms	88.4	69.6-97.5	80.0	48.3-96.7	0.23	0.68 (0.37-0.86)	9.5±53.4
Use of transportation	80.0	55.0-100.0	91.7	45.0-100.0	0.79	0.70 (0.38-0.87)	6.5±53.3
Self care	96.7	76.1-100.0	97.8	52.2-100.0	0.50	0.69 (0.39-0.86)	3.2±42.5
Household activities	95.0	68.4-100.0	90.0	63.3-100.0	1.00	0.99 (0.96-1.0)	13.0±77.7
Leisure and sport	60.0	30.0-86.2	71.7	29.3-93.3	0.06	0.93 (0.83-0.97	-7.1±29.5
Sum score	82.7	47.5-90.2	79.2	49.4-94.8	0.72	0.95 (0.88-0.98)	-0.7±17.4

Interpretation: A p-value >0.05 as assessed by the Wilcoxon signed rank test means that scores on two tests were similar. LOA: Limitis Of Agreement represent mean change in scores of repeated measures (systematic bias) ± 1.96 x standard deviation of these changes (random bias).

Table 4. Pre and post scores and responsiveness of PedHAL and HJHS (n=19)

	Pre		Post					
	Median	**IQR**	**Median**	**IQR**	***p*-Value (Wilcoxon)**	**Mean change**	**SD change**	**SRM**
PedHAL								
Sitting kneeling standing	58.0	44.0-92.5	83.4	41.5-95.8	0.05	9.0	18.3	0.5
Functions of the legs	74.5	44.1-87.5	82.9	46.4-93.4	0.22	1.7	27.2	0.1
Functions of the arms	83.3	69.6-100.0	80.0	61.7-100.0	0.23	-8.1	22.3	-0.4
Use of transportation	76.7	56.7-92.5	80.0	46.7-100.0	0.94	-13.1	37.6	-0.3
Self care	94.5	76.1-100.0	94.5	71.1-100.0	0.48	-1.8	10.7	-0.2
Household activities	80.0	66.7-100.0	76.7	30.0-100.0	0.80	-19.1	42.4	-0.4
Leisure and sport	53.3	31.4-82.9	55.0	36.3-90.7	0.30	6.6	37.9	0.2
Sum score	74.1	49.6-91.6	78.6	54.1-94.8	0.43	2.9	15.5	0.2
HJHS								
Total score	11.0	3.0-19.0	6.0	2.0-11.0	<0.01	-3.3	3.6	-0.9

Interpretation: A p-value >0.05 as assessed by the Wilcoxon signed rank test means that scores on two tests were similar. SRM: standardized response mean.

DISCUSSION

This study describes the psychometric properties of the PedHAL as a measure of functional health status of Romanian children with haemophilia, who are not on intensive replacement therapy. Testing of the PedHAL in 29 consecutive patients with impairments at joint levels and function showed good construct validity. In general, test-retest reliability at the cohort level (ICCs) was good. Alternatively, test-retest agreement of the PedHAL (LOA) showed substantial variability in scores with repeated testing, which makes it less suitable to measure small improvements in functional ability (e.g. due to rehabilitation) at the individual patient level. Romanian Children with haemophilia clearly show impairments in joint health as well as functional ability based on objective measures and self-report.

Score distribution and internal consistency

PedHAL domain and summary scores measured in this population of Romanian children were considerably lower (20-30 points) than in the Dutch children on intensive factor replacement therapy. Despite their young age, the Romanian patients perceived considerable limitations in their functional activities as is reflected by a median score of 83.5 (IQR 47.9-90.5). In contrast the majority of items (55%) in the domain "self-care" were scored as 'never a problem'. This indicates that some items in that domain are not problematic in this population and do not contribute to discriminating patients. In addition there were a high number of activities that were reported to be not applicable (N/A) in the domains of household activities and leisure and sports activities (27 and 48% respectively). Specific items with a high number of NA scores (>30%) and high proportion (>50%) of highest possible scores (ceiling effect) are marked in Appendix I. Future studies should confirm if these items should be retained in the PedHAL or if they are to be omitted. Given the small population that was studied as well as the possible cultural influence on item relevancy, we consider it too early to perform a rigorous item reduction procedure of the PedHAL at this moment.

Values for internal consistency of the domains were very high (Chronbach's alpha = 0.94-0.98) and lower for the domains "functions of the arms" with exception of "use of transportation" (Chronbach's alpha = 0.77 and 0.65 respectively). Lower values for internal consistency for health status indexes are not an indicator of unreliability because a priori there is no assumption made for the homogeneity of the items [18]. Rather it pinpoints the differential effect that haemophilia can have on functional ability. Higher values for internal consistency

(>0.95), on the other hand, may be an indicator of redundancy of items [12]. For the PedHAL this might be the case for the domains "functions of the legs" and "leisure and sport" as well as for the sum score. This means that in these domains some items could be omitted without profoundly affecting the reliability of these domains.

Construct validity

We addressed construct validity by correlating PedHAL scores with three subscale scores of the CHQ-50, joint health (HJHS), functional independence (FISH) and walking ability (6MWT). As expected, we found moderate associations of the PedHAL with joint health (HJHS) (rho=-0.59) which was similar to earlier findings in a Dutch sample (rho = 0.59) [1]. The difference in the direction of the association between the PedHAL and joint health in these two studies is due to the normalization of joint health scores in the Dutch patient sample which reverses the scoring. The association between PedHAL and functional independence (FISH) was a novel comparison and showed moderate association (rho=0.65). This is consistent with findings of Poonnoose et al. [5] who found a correlation of -0.66 of the FISH and adult HAL. The difference in direction of the association was caused by the reversed coding and normalization applied for the PedHAL in this study, compared to raw scores in the study of Poonnoose.

We did not find a significant correlation between PedHAL scores and 6MWT. This could be explained by the fact that the 6MWT only measures one aspect of the patient's functional ability (i.e. walking ability). This finding is inconsistent with the study of van Genderen et al. who found low to moderate associations between the HAL and performance tests (e.g. 50 meter walking test) in adults [19]. Furthermore, it was somewhat surprising to see that the 6MWT and the domain "functions of the legs" did not correlate significantly. When revisiting the data of the heart rate monitoring during the 6MWT, we observed that in general the exercise intensity of the 6MWT was low (54% of expected maximal heart rate). The heart rate after the 6MWT was on average 112 bpm (SD 15) and showed large variation with values ranging from 88 to 145 bpm. Consequently, there was considerable variation in the increase in heart rate during the test (median increase of 23 bpm; IQR=13-35 bpm). These findings suggest that the walking speed during the 6MWT has never reached an intensity that resulted in reaching a maximal cardio-respiratory response. Apart from differences in functional ability there may also have been differences in the motivation of the participants to achieve a maximal performance during the test. This might have hampered finding

associations between the 6MWT and the domain "functions of the legs". Additionally, only 4 items of the domain "functions of the legs" really concern functional walking ability and this may be too little to result in a correlation of the 6MWT with that total domain.

As expected, a significant association was found between the PedHAL and the physical function domain of the CHQ-50 (rho=0.40). Although significant, one would expect a slightly higher association between the PedHAL and the physical function domain of the CHQ-50. For example, in Dutch children, an association of 0.57 was found [1]. We have no clear explanation for this discrepancy, however it could be speculated that there are cultural differences in the way parents or caregivers rate their child's functional ability.

In addition, PedHAL scores did not correlate with the subscales "behaviour" and "mental health" of the CHQ-50 which confirms the physical nature of the PedHAL domains. In summary, these results are in line with earlier findings in a Dutch cohort of children on intensive factor replacement therapy and provide further evidence for the construct validity of the PedHAL applied in children with on-demand therapy.

Reproducibility

Group scores of the PedHAL for test and retest were similar for sum and domain scores, except for "sitting kneeling standing" which showed slightly higher scores on the retest occasion. Furthermore reproducibility of the PedHAL was assessed by relative agreement (ICC) as well as absolute agreement (LOA) [12]. Although the ICC values were high for the entire scale, as well as for the domains "functions of the legs" and "sitting kneeling standing", they were somewhat lower for the domains "functions of the arms" and "self-care". Because ICC values are partly dependent on the distribution of the data, the lower ICC values could be the result of the large proportion of patients scoring the best possible score for many items in these domains (45 and 55% respectively). The consequence of these lower ICC values is that it may be more difficult to distinguish patients e.g. with more or less severe disease based on the sole scores on these domains only [12].

LOA values found in this study were considerably higher than those found in a Dutch cohort [1]. The low LOA values in that study were most probably due to the ceiling effect in that population. The higher LOA values in this study show that there is some test-retest variability in scores that has to be taken into account. LOA values of around 20% of the scoring range are not uncommon for health status questionnaires [20,21]. This observation suggests that individual changes in scores

within the limits of agreement may reflect day-to-day sampling variability and not true clinical change. The clinical relevance of this finding is that if an individual (stable) patient completes the PedHAL twice, then there is a probability of 95% that the second score will be about 15-20 points higher or lower than the first occasion. Only if a change of this magnitude is smaller than the minimal important change (which seems questionable but has yet to be determined) the questionnaire could be useful for individual patient management [12].

Responsiveness

The HJHS was somewhat more responsive to the short rehabilitation programme than the PedHAL. The scores on the PedHAL were not different pre and post treatment. This could be explained by the relatively short period of rehabilitation which may have resulted in only minor improvements in the functional status of these children. Additionally, the recall period of one week also includes a part of the treatment period in which gains could have been made. Already from the data of the test-retest (i.e. LOA for the sum score of 17.4 points) one can observe substantial improvements in functional ability have to be made before one can conclude that there is a "real" change.

Limitations

There are some limitations to this study. Firstly, most children in this study were older than 8 years. Therefore we lack data on younger children. Additional work needs to be done to evaluate the psychometrics in that age group. Secondly, general advice for psychometric analyses is sample sizes of at least 50 patients [12]. Due to time and budget constraints we were not able to include more patients in this study. This emphasizes the importance of global and multiple centre collaborations with regards to the studying outcome in haemophilia patients. Thirdly, the PedHAL is expected to be subject to cultural differences, making some items more or less appropriate for different cultures. This could especially be true for the items in the domains household activities, leisure and sports and transportation. The scoring of the PedHAL now omits 'not applicable' (N/A) items from the normalized score. The exact consequence of large numbers of N/A's is not clear at this moment, but it could be anticipated that future versions of the PedHAL may pose a limit to the number of N/A's (e.g. <20%) of the PedHAL to be considered valid.

Clinical implications

From a clinical perspective, the interpretability of the PedHAL scores has been improved by reporting performance in several subpopulations with clearly different levels of functional health status [12]. We emphasize that when using the PedHAL to track progress for the individual patient, large improvements have to be seen in order to be sure that progress falls outside the natural variation. This is especially true for the domain scores. The PedHAL is not unique in this regard, this is a common "flaw" of health status measures and is not easily solved [22]. The PedHAL could however be used qualitatively to highlight problematic activities for the individual patient. Finally, the absence of perfect correlations between the different instruments used in this study (FISH, HJHS, PedHAL, 6MWT) highlights the fact that they are measuring different aspects of physical functioning. We therefore fully agree with Beeton et al. [23] who state that a combination of impairment measures, both clinical and investigative, self-report- and performance-based functional activities is required to fully assess the impact of haemophilia on the musculoskeletal system.

Future research

We propose that the PedHAL could be improved by removing some of its redundancy to further improve its reliability. Reducing the redundancy of this instrument by deletion of activities may come with a cost of losing content validity. This issue has to be addressed too. Furthermore the content may has to be adapted in some way to make it cultural appropriate when introduced elsewhere. Possibly, the eventual PedHAL will consist of a "common trunk" and additional culture specific activities. We encourage further refinement of this tool by international collaborators to improve the outcome evaluation of the children with haemophilia around the world.

Conclusion

The PedHAL showed good construct validity. In general, test-retest reliability at the cohort level was good, whereas test-retest agreement of the PedHAL showed substantial natural variation in scores with repeated testing. This implies that the PedHAL, as well as many other health status measures, at this moment may be more appropriate for research purposes than for individual patient monitoring in clinical practice. Further adaptation of the PedHAL could enhance this test-retest agreement which might enhance its responsiveness to change in the individual

patient. Romanian children with haemophilia have significant impairments in joint health and function based on objective and self-report measures.

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APPENDIX I: PedHAL

Question:
In the previous week, did you have any difficulty, due to haemophilia, with:

Scoring and recoding:

Answering options	Score	Recode
N/A	8	0
Impossible	1	6
Always	2	5
Usually	3	4
Sometimes	4	3
Almost never	5	2
Never	6	1

Normalization of score:

Domain	Normalization
Sitting/kneeling/standing	$100-((\sum_{1-10} - \text{valid}) * (100/(5*\text{valid})))$
Functions of the legs	$100-((\sum_{11-21} - \text{valid}) * (100/(5*\text{valid})))$
Fuctions of the arms	$100-((\sum_{22-27} - \text{valid}) * (100/(5*\text{valid})))$
Use of transportation	$100-((\sum_{28-30} - \text{valid}) * (100/(5*\text{valid})))$
Self care	$100-((\sum_{31-39} - \text{valid}) * (100/(5*\text{valid})))$
Household tasks	$100-((\sum_{40-42} - \text{valid}) * (100/(5*\text{valid})))$
Leisure activities and sports	$100-((\sum_{43-53} - \text{valid}) * (100/(5*\text{valid})))$

"valid" = number of items scored within the specific domain.
Items with "n/a" responses are to be considered ***not*** valid

Items of the PedHAL:

Sitting/kneeling/standing
1. Sitting down (e.g. on a chair or couch)
2. Sitting on the ground (e.g. when watching television or playing)
3. Standing up from a chair *with* arm rests
4. Standing up from a chair *without* arm rests **
5. Kneeling/squatting (bending your knees)

6. Squatting for long periods (knees not touching the ground)
7. Bending over forwards
8. Standing still for a short period (less than 10 minutes; e.g. waiting in a queue in a shop)
9. Standing still for longer periods (from 10 minutes to 1 hour)
10. Standing still for very long periods (more than 1 hour)

Functions of the legs

11. Walking short distances (less than 10 minutes) **
12. Walking longer distances (from 10 minutes to 1 hour)
13. Walking long distances (more than 1 hour)
14. Walking on an uneven surface (e.g. a bumpy road, high curbs, doorsteps)
15. Walking on a soft surface (e.g. on the beach)
16. Strolling (e.g. a day at the zoo)
17. Running (e.g. to catch the bus, or catch up to a friend)
18. Jumping (onto/off something)
19. Walking *up* stairs (a whole stairway is around 14 steps)
20. Walking *down* stairs
21. Walking or riding up a small hill or slope without help

Fuctions of the arms

22. Carrying large or heavy objects with two hands (e.g. a big box of toys, a pile of books)
23. Stretching to reach something above your head (such as a high shelf)
24. Fine hand movements (e.g. picking up Lego, playing computer games) **
25. Writing (such as schoolwork or homework)
26. Leaning on your arms
27. Shaking hands with someone **

Use of transportation

28. Cycling
29. Getting in and out of the car **
30. Using public transport (bus, train, metro, tram)

Self care

31. Drying your entire body **
32. Putting on a t-shirt, jumper or sweater, etc. **

33. Putting on trousers **
34. Putting on shoes and socks **
35. Wiping your bottom after using the toilet **
36. Fastening a hood or doing up the top button on your jacket **
37. Buttering bread or making a sandwich **
38. Unscrewing the lid from a bottle of water, juice, etc. **
39. Brushing your teeth **

Household tasks

40. Chores in the house (e.g. making your bed, cleaning your room, setting the table)
41. Outside chores (e.g. putting the rubbish out, washing the car)*
42. Other household chores (running errands, walking the dog)*

Leisure activities and sports

43. Going out and dancing (theatre, museum, cinema, pub, disco)
44. Playing outside, alone or with others
45. School sports: exercises and gymnastic equipment
46. School sports: athletics (e.g. long jump)*
47. School sports: ball sports (volleyball, softball)*
48. Playing non-contact team sports (e.g. volleyball, basketball)*
49. Playing contact team sports (e.g. water polo, soccer)*
50. Individual non-contact sports (e.g. tennis, cycling)
51. Individual contact sports (judo, karate, boxing, kickboxing)*
52. Taking part in a sports event over the course of several days (e.g. swimming, walking, cycling or a sports tournament)*
53. Going to school camp or summer camp

Legend:
* >30% of the patients responded with “not applicable” to this item
** >50% of the patients scored the highest possible score for this item

Chapter 5

Habitual Physical Activity in Dutch Children and Adolescents with Haemophilia

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SUMMARY

For patients with haemophilia, a physically active lifestyle is important to maintain musculoskeletal health and to prevent chronic diseases, such as cardiovascular disease. Therefore, we studied physical activity levels, in Dutch children and adolescents with haemophilia as well as its association with aerobic fitness and joint health.

Forty-seven boys with haemophilia (aged 8–18) participated. Physical activity was measured using the Modifiable Activity Questionnaire (MAQ) and was compared with the general population. Aerobic fitness was determined using peak oxygen uptake per kilogram body mass (VO_2peak/kg). Joint health was measured using the Haemophilia Joint Health Score (HJHS). Associations between physical activity, joint health and aerobic fitness were evaluated by correlation analysis.

Subjects were 12.5 (SD 2.9) years old, had a Body Mass Index (BMI) of 19.5 (SD 3.1; z-score 0.5) and a median HJHS score of 0 (range 0-6). Cycling, physical education and swimming were most frequently reported (86%, 69% and 50% respectively). Children with severe haemophilia participated significantly less in competitive soccer and more in swimming than children with non-severe haemophilia. Physical activity levels were similar across haemophilia severities and comparable to the general population. VO_2peak/kg was slightly lower than healthy boys (42.9±8.6 vs. 46.9±1.9 mL/kg/min; p=0.03). Joint health, aerobic fitness and physical activity showed no correlation.

Dutch children with haemophilia engaged in a wide range of activities of different intensities and showed comparable levels of physical activity to the general population. Aerobic fitness was well preserved and showed no associations with physical activity levels or joint health.

INTRODUCTION

Children with chronic disease are notoriously at risk for a physically inactive lifestyle due to realistic or perceived barriers [1]. Children with haemophilia may be no exception to this notion. An active lifestyle is important because it has numerous health benefits, especially for primary and secondary prevention of chronic diseases (e.g., cardiovascular disease, diabetes, cancer, hypertension, obesity, depression and osteoporosis) and premature death [2]. For patients with haemophilia physical activity even has additional benefits for musculoskeletal health including an increase in range of motion [3], reduction of the number of joint bleeds [4] and improvement of strength and proprioception [5]. The need for a physical active lifestyle in patients with haemophilia is further highlighted by the finding that bone mineral density in children with severe haemophilia (FVIII/IX < 1%) is lower than in normal subjects [6].

Currently a positive trend is observed in which children with haemophilia are increasingly encouraged to participate in physical activities and sports [7,8]. For example a survey of Dutch adults with haemophilia showed that those on prophylactic treatment had a higher proportion was active in swimming and cycling [9]. In addition, it was noted that the attitude towards sports among patients with haemophilia has improved, and that the range of practiced sports has increased, most likely due to improved medical treatment [7]. Despite the increased participation in sports, aerobic fitness of children with haemophilia is still reduced compared to healthy peers [10].

One explanation for reduced aerobic fitness could be reduced participation in vigorous activities by children with, especially severe, haemophilia, as has been reported for children with Cystic Fibrosis (CF) [11]. Until now, no studies have looked in detail into the intensity level of self-reported activities in children with haemophilia as well as its relationship with aerobic fitness. Recently, Buxbaum et al. reported decreased self-efficacy scores compared to healthy children [12]. The authors however did not report on the association of intensity of exercise to direct aerobic fitness.

Therefore, the present study was aimed at 1) describing type and intensity of physical activity, in children and adolescents with haemophilia, and 2) assessing the relationship between physical activity, joint health, and aerobic fitness.

MATERIALS AND METHODS

Subjects

109 Patients were contacted directly or by phone to participate in this study. Forty-eight (44%) agreed to participate and 1 boy was excluded from analyses post hoc, after being diagnosed with an unspecified muscular disorder. Eventually, forty-seven children between 8 and 18 participated in this study, performed in summer and fall of 2006. Twenty-one suffered from severe, 7 from moderate, and 19 from mild haemophilia. The patients were all treated at the Van Creveldkliniek, University Medical Center Utrecht, the Netherlands. All children with severe haemophilia, as well as 4 with moderate haemophilia were on a prophylactic treatment regime while the others were treated on-demand. None of the patients had an active bleed at the time of testing and patients with moderate and severe haemophilia received prophylactic treatment in the 24 h preceding testing. All subjects and their parents were fully informed and informed consent was obtained. The study protocol was approved by the Ethical Review Board of the University Medical Center, Utrecht.

Joint Health and anthropometrics

Joint health of ankles, knees and elbows was measured by the Haemophilia Joint Health Score (HJHS version 1.0). This instrument has been developed and validated recently by the International Prophylaxis Study Group (IPSG)[13]. The HJHS was designed as a more sensitive version of the orthopaedic joint score by Gilbert [14], it consists of eleven items for all six joints (swelling, swelling duration, muscle atrophy, axial alignment, crepitus, flexion loss, extension loss, instability, pain, strength and gait) and global gait. The scoring scale ranges from 0 to 144 with a score of zero representing best possible joint health. All the measurements of the HJHS were performed by two senior paediatric physical therapists. Weight was measured with an electronic scale and height was measured with a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight/height^2. Height, weight and BMI were compared to Dutch reference values [15].

Physical activity

Physical activity was measured with the Modifiable Activity Questionnaire (MAQ). This questionnaire has been shown to be a valid and reliable instrument for the measurement of habitual physical activity in children [16]. First, subjects had to indicate in how many and which sports activities they had participated in at

a competitive level. Then, all activities in which the child participated at least 10 times during the past year were reported. Patients could also report activities that were not on the list. For each activity that was indicated, subjects were asked to provide detailed information on the number of times per month and the average duration of participation (hours per time) for each activity. The total hours of activity were summed and expressed as an average of the total hours of activity per week for the past year (TOT-hrs/week). For each activity, a rough estimate of its relative intensity was derived by multiplying the average hours per week by the metabolic cost of that activity (obtained from existing tables by Ainsworth et al. [17]). Relative intensity was expressed as Metabolic Equivalent Transformation (MET)-hrs/week. 1 MET is equivalent to the energy expenditure in rest (i.e. sitting on a chair). The number of hours that subjects engage in vigorous (VIG) activities (i.e. >6 MET) were calculated and expressed as VIG-hrs/week. The participation of children in competitive sports was compared with Dutch contemporaries as provided by the Dutch Social and Cultural Planning Bureau [18].

Physical activity recommendation for the Dutch population

Data of physical activity were compared to that of the general Dutch population at the time of performing this study [19]. For children under 18 the Dutch recommendation for Healthy Physical Activity requires one hour of moderate physical activity (i.e. 5-8 MET) per day [20]. For this study we rated children as "active" if they had exercised an extended period (the past 12 months), at least 5 days per week, one hour a day at ≥ 5MET. Children were classified "inactive" if they did not reach the recommended daily norm (i.e. one hour of activity (≥ 5 MET) on one single day of the week. The remaining children were classified as "semi-active".

Aerobic fitness test

All subjects performed a graded exercise test using an electronically braked cycle ergometer (Lode Corrival, Lode BV, Groningen, the Netherlands). The seat height of the ergometer was adjusted to the patient's leg length. After 1 min of unloaded cycling, workload was increased with 15 or 20 Watt (depending on height of the patient) every minute according to the Godfrey protocol [21]. The test was stopped when patients were unable to maintain a cadence of 60 revolutions or when they gave up, despite verbal encouragements. During the test, patients breathed through a facemask (Hans Rudolph Inc., Kansas City, MO, USA), which was connected to a calibrated gas analysis system (Cortex-Metamax Cortex-medical GmbH, Leipzig,

Germany). This system permits measurement of oxygen uptake (VO_2) and carbon dioxide production (VCO_2). Respiratory exchange ratio (RER) was calculated as VCO_2/VO_2. Heart Rate (HR) was measured continuously by a three-lead electrocardiogram (Hewlett-Packard, Amstelveen, the Netherlands).

Peak HR and peak work rate were defined as the highest value measure (10 second intervals). Absolute peak oxygen uptake (VO_2peak) was defined by the average value over the last 30 seconds of the maximal exercise test. Relative VO_2peak (VO_2peak/kg) was calculated as absolute VO_2peak divided by weight. Peak values for oxygen uptake and work rate were compared with Dutch reference values [22].

Statistics

All analyses were performed with SPSS (version 15). Patient characteristics, height, weight and BMI were expressed as z-scores which reflect the difference between patients and their age matched healthy peers. These characteristics were also compared between haemophilia severities using independent samples T-test or the Mann-Whitney test depending on the distribution of the data. The HJHS (highly skewed), and MAQ data were compared by the Mann-Whitney test. Difference in physical activity participation was tested by a Chi square test. Associations between physical activity and aerobic capacity were calculated by Spearman correlation coefficient. A *p*-value less than 0.05 was considered statistically significant. Data were expressed as means ± standard deviation (SD) or as median and Interquartile range (IQR) were appropriate.

RESULTS

Subjects

Subject characteristics are presented in Table 1. Subjects were 12.5 (SD 2.9; range 8.2-17.4) years old, had a BMI of 19.5 (SD 3.1; Z-score 0.5) and had a median HJHS score of 0 (range 0-6). Height, weight and BMI did not differ from Dutch reference values. After adjustment for age by calculating z-scores, only weight was different across severities: non-severe patients were heavier.

Table 1 : Subject characteristics

Variable	Total (n=47)	Non-severe (n=26)	Severe (n=21)	*P*-value
Age (years)	12.5 ± 2.9	13.2 ± 2.6	11.7 ± 2.9	NS
Height (m)	1.59 ± 0.17	1.65 ± 0.15	1.52 ± 0.17	0.01
z-score	0.2 ± 0.9	0.3 ± 0.8	-0.1 ± 1.0	NS
Weight (kg)	50.8 ± 15.8	56.3 ± 13.4	44.1 ± 16.3	<0.01
z-score	0.5 ± 1.1	0.8 ± 1.1	0.1 ± 1.0	0.04
BMI	19.5 ± 3.1	20.6 ± 2.8	18.3 ± 3.1	0.01
z-score	0.5 ±1.0	0.8 ± 1.1	0.2 ± 0.9	NS
HJHS	0 (0-6)	0 (0-4)	0 (0-6)	NS

Legend: Data are shown as means ± SD for all variables except for HJHS which is shown as median (range). The P-value refers to the comparison between non-severe and severe patients. NS: not significant.

Physical activity

Thirty-six MAQ questionnaires were adequately completed and used for analysis. Age and proportion of severe patients did not differ between the patients for whom a MAQ was available and the other patients. Children with haemophilia reported engagement in a wide variety of activities. Thirty out of 36 (83%; non-severe n=21; severe n=15) children indicated to have engaged in one or more activities at a competitive level. There was no difference between non-severe and severe patients with regard to the number of sports involved in (1 (IQR 1-3) vs. 1 (IQR 0-2) respectively; p=0.09). The activities that were participated in at a competitive level most frequently were: football (n=13; 36%), swimming (n=6; 17%), tennis (n=4; 11%), cycling (n=3; 8%), basketball (n=2; 6%) and track and field (n=2; 6%). Children with non-severe haemophilia participated more in football than those with

severe haemophilia (52% vs. 13%; p=0.04). For the other activities no statistical difference were found between the groups. The top five (competitive) sports that boys aged 6-18 in the Netherlands participated in during the same year of study was: football (58%), swimming (58%), football (indoor; 24%) , running (22%) and table tennis (19%) [18].

Figure 1 shows all activities that at least two patients participated in during the last year. The top five consisted of cycling (86%), physical education (69%), swimming (50%), football (30%) and fitness (19%). A higher proportion of children with severe haemophilia participated in swimming than those with non-severe haemophilia (73% vs. 33% respectively, p=0.01). No differences were found in leisure activity participation for the other activities.

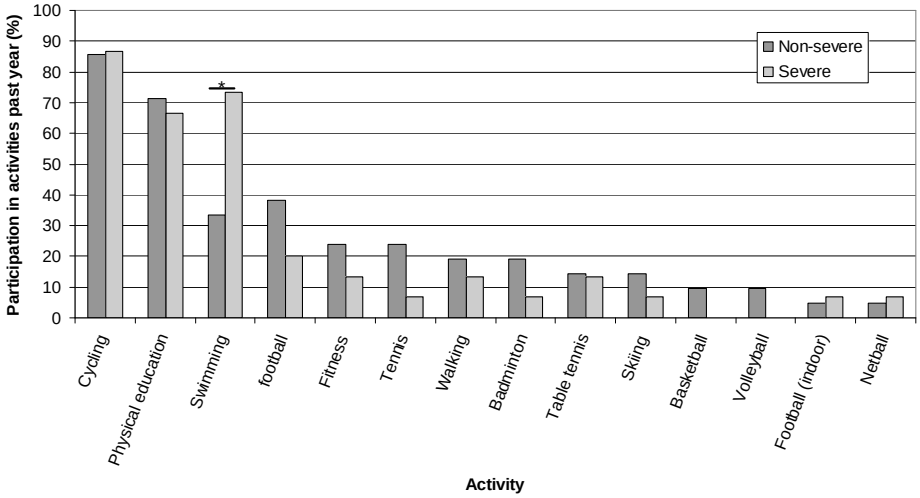

Figure 1. Activities children participated in during the past year. Data are shown as percentages of the total group. Only those activities that were engaged in by more than 2 children are shown. * Significant difference between severe and non-severe (p = 0.03).

The calculated physical activity-related energy expenditure of past year activities (n=36) can be appreciated from Figure 2. There were no differences between haemophilia severity subgroups for total hours per week (8.7±3.8 vs. 8.6±7.8), MET-hours per week (54.9±30.3 vs. 55.6±53.4) or vigorous-hours per week (6.2±4.2 vs. 5.4±6.3).

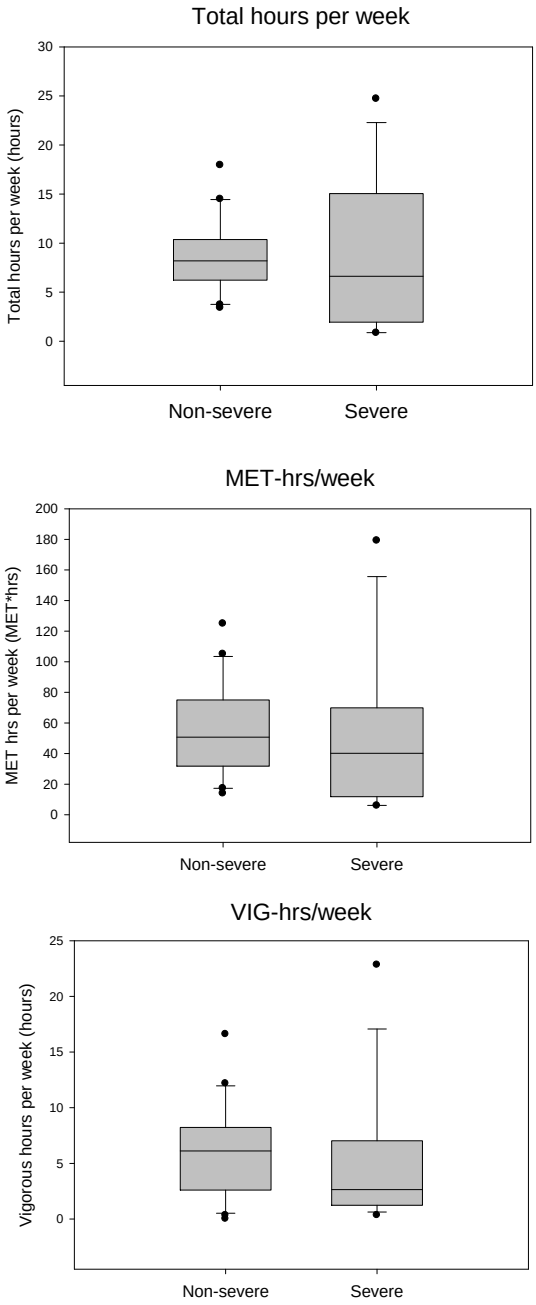

Figure 2. Box and whisker plots of Total hours (top) MET-hours (middle) and vigorous hours (bottom) of physical activity per week for patients with non-severe and severe haemophilia. The boxes represent the 25th to 75th percentile, the whiskers represent the 5th and 95th percentile and the dots are outliers.

When data of the MAQ were compared to the Dutch public health recommendations for healthy physical activity, only 27.8% reached the recommended level of daily physical activity. This is slightly higher than the general Dutch population of which 21% of the boys (aged 4-17 years) reached this level [19]. Likewise, the level of inactivity (8%) in boys with haemophilia was lower than in the general population (12%).

Aerobic fitness

Results of the aerobic fitness test are provided in Table 2. All 47 patients were able to complete aerobic fitness test without any adverse events. Absolute values of peak work rate and VO_2peak was similar between patients and Dutch reference values. VO_2peak/kg for the total group was slightly lower than Dutch reference values (42.9 ± 8.6 vs. 46.9 ± 1.9; p=0.03). Peak work rate and peak oxygen uptake were higher in non-severe than in severe patients.

Relationship between physical activity, aerobic fitness and joint health

No significant correlations were observed between physical activity (TOT-hrs, MET-hrs and VIG-hrs) and measures of aerobic fitness (absolute and relative VO_2peak as %predicted) or joint health (HJHS). All correlation coefficients were very low, ranging between -0.27 and 0.28.

Table 2: Outcome of the aerobic fitness test and comparison with Dutch reference values

	Total (n=47)	Non-severe (n=26)	Severe (n=21)	P-value
RER_{peak}	1.22 ± 0.16	1.19 ± 0.11	1.26 ± 0.20	NS
Peak Heart Rate (beats/min)	191 ± 11	191 ± 12	190 ± 10	NS
Peak work rate (Watt)	183 ± 75	207 ± 79	151 ± 56	<0.01
% predicted for heigth	108 ± 18	109 ± 19	107 ± 16	NS
Peak work rate/kg (Watt/Kg)	3.6 ± 0.8	3.6 ± 1.0	3.5 ± 0.6	NS
% predicted for height	103 ± 23	102 ± 26	104 ± 19	NS
VO_{2peak} (L/min)	2.18 ± 0.85	2.43 ± 0.86	1.88 ± 0.75	0.03
% predicted for height	94 ± 15	95 ± 15	93 ± 14	NS
VO_{2peak}/kg (mL/kg/min)	42.9 ± 8.6*	42.7 ± 9.8	43.1 ± 7.0	NS
% predicted for age	91 ± 17	90 ± 19	93 ± 14	NS

Legend: * significantly different from Dutch reference values (p = 0.03). NS: not significant.

DISCUSSION

This cross-sectional study shows that Dutch children engage in a wide range of activities of varying intensities. Physical activity levels were similar across haemophilia severities and comparable to the general population. In addition, children with severe haemophilia participated more in swimming and less in competitive football than children with non-severe haemophilia. Furthermore, aerobic fitness was comparable to Dutch reference values with exception of a slightly reduced oxygen uptake relative to weight. Joint health, aerobic fitness and physical activity showed no significant association/relation.

The children in this study were as active as the general population. This is not a common finding in children with chronic disease. Reduced physical activity levels have been reported in many conditions such as children and adolescents with Juvenile Idiopathic Arthritis [23,24], Cerebral Palsy [25,26] and Spina Bifida [27]. This relatively high level of activity is good news for the patients, as there is evidence that inactivity in children with haemophilia increases the risk of low bone mineral density. For example, a study of Tlacuilo et al. showed a significantly reduced bone mineral density , due to inactivity, in Mexican children with haemophilia who were treated on-demand (Odds ratio 3.2) [28]. The relatively

high level of activity measured in our study, is also good news with regard to the prevention of other secondary chronic diseases such as cardiovascular disease, diabetes, cancer and so on. So with reduced morbidity of the musculoskeletal system, as seen in children on prophylaxis, attention may partly shift to health-related fitness and prevention of secondary diseases. An increasing positive attitude towards participation in physical activity will help to reach the goal of keeping these patients in optimal physical condition. It has to be noted however, that still the majority of the Dutch children (both healthy and those with haemophilia) do not meet the public-health recommendations for healthy physical activity [19]. Therefore, continuous efforts of policy makers will be needed to combat the widespread problem of reduced physical activity among children and adolescents in the Netherlands.

In children with Cystic Fibrosis decreased aerobic fitness was accompanied by reduced participation in vigorous activities. Children with CF participated 2.0±2.5 hours of vigorous activities whereas controls spent 3.7±2.8 hours in that range ($p=0.014$). However, total hours per week (8.6 vs. 8.5) and MET-hrs/week were similar (43.4 vs 49.7) [11]. We found distinctly higher values for hours of vigorous activity than the healthy controls of that study (6.2±4.2 hours in non-severe and 5.4±6.3 hours in severe patients). This could be explained by the high number of children that reported cycling. Cycling contributes to the hours of vigorous activity, as it is rated with an intensity of 8 MET [17].

Participation rates in competitive sports appeared to be low compared to the general population. Only 13% of the children with severe haemophilia participated in competitive football, compared to 52% of the non-severe group and 58% of the normal population. Even when leisure activities are taken into account, only 20% of the children with severe haemophilia participated in football. On the contrary, of those with severe haemophilia, a large proportion participated in swimming, and this proportion was notably larger than in children with non-severe haemophilia (73% vs. 33% respectively). Together these findings seem to indicate that most children with severe haemophilia in this study may avoid sports with a relatively high risk of bleeding episodes; however they were participating in vigorous activities as frequently as the general population. We did not investigate directly if the patients were satisfied with the sports and activities they were currently performing. However an earlier study showed that Dutch boys regret that their parents or their physicians did not allow them to play football [29]. In a recent study in Dutch children, Köiter et al. found a top 5 of sports to be football, swimming, tennis, gymnastics, and cardio-fitness. For Dutch contemporaries they

found the top-5 to be football, gymnastics, tennis, hockey, and swimming. The authors suggested that, probably related to sport counselling advice by their physician, children with haemophilia may have chosen other types of sports activities [8]. This may well be the case in our population too.

Compared to healthy peers [30], aerobic fitness was well preserved with the exception of VO_2peak/kg body weight. A recent Australian study reported a similar observation, although the outcome measure used (number of laps achieved during a shuttle run test) may be less sensitive as the gold standard (VO_2peak) [31]. The reduced VO_2peak/kg is most probably due to a combination of slightly lowered absolute values of aerobic capacity and slightly higher values for body weight. The resulting reduced VO_2peak/kg could limit performance in weight bearing activities, such as running and stair climbing. Therefore, monitoring and active counselling to reduce body weight in overweight subjects remains an important aspect in the follow up of the children with haemophilia.

The absence of an association between joint health and aerobic capacity could be explained by the fact that joint health was nearly optimal in our population resulting in joint health scores (HJHS scores) that are distributed very homogeneously (many scores were zero's). When joints are affected more, we would anticipate a moderate to strong association with declined physical activity participation and aerobic fitness. Clearly the boys in this study on intensive replacement therapy have high levels of joint health. Besides, other factors may also influencing physical activity participation (e.g. psychosocial variables, socio economic and cultural factor). The lack of association between physical activity and aerobic capacity in this study could be explained by the relative rough measure of physical activity measured over the past year. The self- reported questionnaire used in this study may not inform us on the precise intensity of the physical activity that would lead to training effects in these children. Detailed measurement of heart rate responses to physical activities with heart rate monitors would probably give a better insight into the precise intensity of physical activities performed and would most probably lead to better association between physical activity level and aerobic capacity.

A key question is: how much longer should we restrict children with haemophilia who are on prophylactic treatment to participate in contact sports like football? Especially, since recent studies indicate that children with haemophilia on prophylaxis can safely engage in vigorous activities or high impact sports. For example Ross et al. showed that children with haemophilia on prophylaxis participating in high impact sports did not have an increased number of joint

bleedings or target joints [32]. In line with this observation, others failed to find an association between engagement in vigorous activities and bleeding frequency [33]. These results could indicate that we are being too restrictive in allowing specific groups of our boys to participate in physical activities. Future studies may focus on children without prophylactic treatment in order to determine the risks of (non-)contact physical activities in this population.

Limitations and future directions

The population described in this study comes from one single centre. The exercise participation of this population may be different from participation rates in patients treated in other haemophilia treatment centres. Some centres may be more liberal or more conservative in this regard than others. Although we compared anthropometrics, aerobic fitness, physical activity levels, and type of activities with Dutch reference values, we acknowledge the fact that a direct control group of age-matched peers would have strengthened this study.

Furthermore, although the MAQ has shown to be reliable and valid, there is a possibility for recall bias in all physical activity questionnaires [34]. This may be overcome by the concurrent use of more objective measures of physical activity related energy expenditure, such as accelerometry. The MAQ however has an important advantage over accelerometry as it makes clear what type of activity children were involved in (e.g. high risk / low risk). Because accelerometers roughly count accelerations of the body's centre of mass, it is (yet) impossible to distinguish different activities from the data. This drawback favours the use of questionnaires in patients with haemophilia. More prospective studies are needed to elucidate the causal relationship between (types of) physical activities and bleeding episodes in children with haemophilia. Hopefully this will provide better insight into the risks that children with haemophilia encounter during the participation in physical activity.

Conclusion

Dutch children with haemophilia show levels of physical activity that are comparable to those reported by their healthy peers. However, almost 75% of the patients were not meeting public health recommendations for healthy physical activity. Typical recommended activities were performed (cycling, swimming), but also contact sports such as football. More than 70% of severe patients participated in swimming and only 20% in football. Aerobic capacity was well preserved and showed no associations with physical activity levels or joint health.

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Chapter 6

Exercise interventions in patients with haemophilia: a systematic review

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Submitted for publication

SUMMARY

Haemophilia has serious consequences for the musculoskeletal system and functional health status of patients. Exercise might be a useful intervention to counteract the detrimental effects of haemophilia. The aim of this study is to systematically review the literature to determine the effectiveness of exercise interventions in patients with haemophilia.

An extensive search in PubMed, CINAHL, EMBASE, Cochrane and PEDro was performed up to January 2011. Studies with controlled and uncontrolled designs were included. Data on study design, study participants, intervention characteristics and effects were extracted. A best-evidence synthesis, based on the study design, methodological quality (modified Newcastle-Ottawa Scale), and significant findings, was performed. Outcome measures used were reported and grouped into the corresponding level of the International Classification of Functioning, disability and health (ICF).

Initial search of the databases yielded a total 607 records. After removal of duplicates and irrelevant items 23 studies were read in full text. After applying our inclusion criteria 9 studies were included in this review. The studies generically were classified as low level of evidence and had low methodological quality. Exercise interventions were poorly described in most studies. The outcome measures used in most studies often focused on the ICF level “body functions and structures” and to a lesser extent on the level of “activities”. No study included an outcome measure on the level of “participation”

Although we observed many positive effects of prescribed exercise intervention, the methodological quality and level of evidence of the included studies was low. More high quality intervention studies as well as consensus on a core-set of outcome measures are needed to strengthen the evidence-base for exercise for patients with haemophilia.

INTRODUCTION

Haemophilia is characterised by repeated joint bleeds, which may eventually lead to crippling arthropathy. This in turn leads to a circle of deconditioning resulting in a decrease of physical performance. There are numerous studies showing the detrimental effects that haemophilia has on various physical functions such as reduction of muscular strength [1-4], joint flexibility [5], aerobic [6-10] and anaerobic capacity [2]. These reduced physical functions restrict patients with haemophilia in the performance of activities of daily living [11,12] and may lead to a reduced quality of life [13-15]. These negative consequences call for effective treatments to prevent or (partly) reverse the loss of function. Besides adequate factor replacement therapy, physical exercise could be of great benefit to these patients.

Thus far there have been several narrative reports that recommend the use of exercise and/or physical therapy in the treatment of patients with haemophilia [16-19]. Additionally some retrospective studies have reported conflicting results on the effectiveness of physical exercise in haemophilia: For example Harris and Boggio found that those who regularly performed regular physical exercise (i.e. ≥ 3 days per week) had better joint mobility than those who were less active exercise [20]. In contrast with Harris and Boggio, Santavirta et al. did not found an effect on functional ability over a time course of three years in patients receiving physical therapy [21]. The evidence base of this type of studies in general is limited and insufficient in today's 'evidence based practice'.

It is only recently for the last five years that more rigorous studies have been performed in this field to show the potential benefits of physical exercise interventions in haemophilia. Recently, an extensive review was published on this topic [22], but unfortunately it lacked clear descriptions of exercise intervention parameters, as well as an explicit evaluation of study quality and an attempt to systematically summarize the evidence by means of a best evidence approach.

The aim of the current review is to comprehensively present and systematically evaluate the available evidence regarding exercise training interventions in haemophilia patients. The specific research questions of this study are: (1) what exercise interventions are reported, what are their characteristics, what is their methodological quality and what are the reported effects? (2) What types of outcome measures are used to assess the effects of these exercise interventions?

METHODS

Search strategy and selection criteria

Publications were selected based on a literature search up to January 2011 using the PubMed, CINAHL, EMBASE, Cochrane, and PEDro database. Search terms that were used were: 'hemophilia', 'haemophilia', 'coagulopathy', 'rehabilitation', 'training', 'exercise', 'exercise therapy', 'exercise training', 'physical therapy', 'physiotherapy', 'physical fitness', 'aerobic training', 'strength training', and 'resistance training' were used. References of the selected papers were tracked and the related articles function of PubMed was used to find additional publications on this subject. A first screening of titles and abstracts was performed and irrelevant or duplicate articles were discarded. The remaining studies were read in full text and studies were excluded if they did not meet our inclusion criteria. These inclusion criteria were: (1) patients with haemophilia of any age, including all types (haemophilia A and B) and severities of disease (mild, moderate and severe), (2) therapeutic exercise intervention (exercise programmes focusing on muscle strength, cardiovascular fitness, flexibility or a combination), and (3) inclusion of outcome measures on the level body functions and structures, activities or participation according to the International Classification of Functioning disability and health (ICF [23]). Exclusion criteria were (1) reports published in books, (2) conference proceedings or abstracts (3) case studies, and (4) retrospective studies. No publication date or language restrictions were imposed.

Data extraction

Data on study design, study participants, intervention characteristics and effects were extracted by one author (WG). The outcome measures used in the studies were categorized using the ICF framework for the description of health [23]. In this framework, a person's disability can be considered in terms of impairment on the body structure of functions level, activity limitations and participation restrictions.

Methodological Quality

The methodological quality of each included study was critically appraised. Each study was assessed according to the likelihood that bias, confounding and/or chance may have influenced its results [24]. For this review the methodological quality of studies was assessed with the Newcastle – Ottawa quality assessment scale (NOS) for non randomized studies'. This scale is specifically designed to evaluate the risk of bias in non-randomized studies for systematic reviews and meta analyses [25]. This scale was modified for the purpose of the study [26] so that it

includes items specific for evaluation of exercise training studies (Appendix A). The score per item is either 1 or 0 resulting in a total score ranging from 0 to 9. In literature a cut-off value for high versus low quality of 5 [27] or 6 points [28] are reported. In this review a cut-off value of 5 or higher was chosen for a study to be high quality. Quality assessment was performed by two independent reviewers (WG and TT). Whenever there was disagreement consensus was brought by a third reviewer (JN).

Best evidence synthesis

Because of the heterogeneity, in terms of interventions and outcome measures, a quantitative synthesis (meta analysis) was impossible. To meet our aim and present a comprehensive analysis of the available studies we performed a best-evidence synthesis based on the classification of the quantity, level and quality (risk of bias) of the included studies.

The quantity of evidence reflects the number of the studies that have been included in the evidence base. The quality of evidence was determined as outlined in the previous paragraph. The level of evidence was determined as follows: Each study design was assessed according to its place in the research hierarchy of the National Health and Medical Research Council (NHMRC additional levels of evidence and grades for recommendations for developers of guidelines) [24]. This hierarchy reflects the potential of each study included in the systematic review to adequately answer a particular research question, based on the probability that its design has minimised the impact of bias on the results [24]. The most appropriate study design to answer each type of clinical question (intervention, diagnostic accuracy, aetiology or prognosis) is level II evidence. Level I studies are systematic reviews of the appropriate level II studies in each case. Study designs that are progressively less robust for answering each type of question are levels III and IV [24]. Level II studies are randomised controlled trials. Level III studies are subdivided in three sublevels: level III-1 are pseudorandomised controlled trials (e.g. alternate allocation or some other method), level III-2 are comparative studies with concurrent controls (e.g. non-randomised experimental trial, cohort study), and level III-3 are comparative studies without concurrent controls (e.g. historical control study). Level IV studies are case series with either post-test or pre-test/post-test outcomes.

Finally, the evidence base was determined for all outcome measures and could result in one of the four following components: A (excellent; several level I or II studies with low risk of bias), B (good; one or two level II studies with low

risk of bias or a systematic review / multiple level III studies with low risk of bias), C (satisfactory; level III studies with low risk of bias), and D (poor; level IV studies, or level I to III studies with high risk of bias).

RESULTS

Search results and selection of studies

Initial search of the databases (Fig. 1) yielded a total 607 records. Reference tracking resulted in an additional 4 potentially relevant studies. Consequently, we excluded 588 records based on title and abstract and/or because they were duplicate. The remaining studies (n=23) were read in full-text and 14 were excluded because they did not meet our inclusion criteria: 4 were case studies, 1 was a retrospective study, 3 were abstracts and 6 were not intervention studies. Eventually, 9 studies in 160 unique patients were included in this review.

Study design and subject characteristics

Of the 9 included studies, five were case series and four were non-randomized experimental trials. No randomized controlled trials were found on this topic. In Table 1 the study design and subject characteristics are shown. Of the non-randomized experimental studies, two had a passive control group consisting of healthy subjects [29,30], one had a healthy control group who performed the same programme as patients [31] and one included both an active and passive healthy control group [32]. Evaluations were performed both before and after the total training programme for all studies except for the study of Garcia et al. [31] in which measurements were taken pre and post every single session. The evidence level of the included case series was level IV (lowest level) and the non-randomized experimental studies are assigned level III-2 evidence according to the NHMRC ranking [33]. The number of patients studied was relatively small ranging from 9 [31,32] to 32 [34]. The age of the patients included in selected studies ranged between 5 and 62 years old. Four studies concerned patients with haemophilia-A [29,30,32,35], three studies included both patients with haemophilia-A or B [34,36,37], and two studies did not report the type of patients studied [31,38]. The majority of the included patients had severe haemophilia (n=121; 76%) and fewer patients with moderate or mild haemophilia were included (n=32; 20% and n=7; 4% respectively). Co morbidities of patients were reported in two studies [35,38] and included HIV, hepatitis C, diabetes, fibromyalgia, neurofibromatosis, osteopenia, osteogenesis imperfecta and cancer.

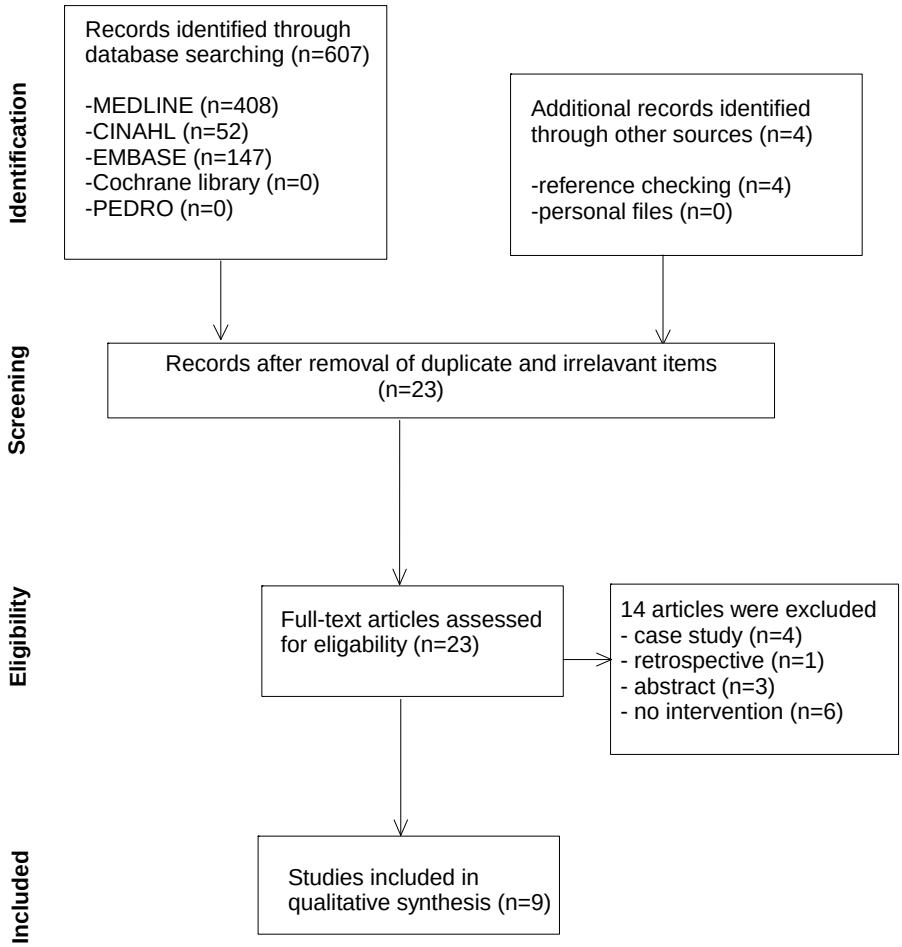

Figure 1: Flowchart of study selection procedure

Methodological quality

The methodological quality of the studies was poor with a median score of 2 (Interquartile range 1.5-3) out of 9 (Table 2). Criterion 8 (valid test method used for measuring physical fitness), was met by all studies. Criterion 1 (selection of a homogeneous patient group) was met by only five studies [29,30,32,34,35], criterion 3 (reproducibility of the training program) was also met by five studies [29,30,34,35,38], and criterion 9 (assessment of quality of life and/or functional capacity by valid questionnaire) was met by one study [37]. The remaining criteria (2,4,5,6, and 7; Table 2) were not met by one single study.

Table 1: Study design and subject characteristics

Study	Year	Age (years)	N	Type and severity	Treatment	Comorbidities	Number of groups	Time and number of measurements	Design according to the NHMRC	Level of evidence according to the NHMRC
Greene [34]	1983	20.8; range 7-51	32H	24 severe A; 3 mod A; 5 severe B	On demand	NR	1	Before and after 6 months training	case series	IV
Hilberg [32]	2003	32.4 (SD 9.4) range 16-44	9H/8AHC/ 11PHC	9 severe A	not clearly described	NR	3	Before and after 6 months training	non-randomised experimental trial	III-2
Querol [30]	2006	H:36.1(SD 4.5) Range 20-62; HC:34.7(4.1) Range 17-58	10H/10HC	10 severe A	Factor infusion before study was carried out	NR	2	Before and after 6 weeks of training	non-randomised experimental trial	III-2
Gurcay [36]	2008	13.0 (SD 4.3) range 3-18	31H	4 severe A; 2 severe B; 17 moderate A; 4 moderate B; 4 mild A	prophylaxis during training period (Factor VIII: 20 IU/kg, 3 times per week; Factor IV: 20 IU/kg, 2 times per week)	NR	1	Before and after 4 weeks of training	case series	IV
Gomis [29]	2009	H: 34.9 (SD 2.1) range 23-44 HC: 29.1 (2.9) range 19-59	15H/15HC	15 severe A	On demand	NR	2	Before and after 8 weeks of training	non-randomised experimental trial	III-2

Table 1: Study design and subject characteristics (continued)

Study	Year	Age (years)	N	Type and severity	Treatment	Comorbidities	Number of groups	Time and number of measurements	Design according to the NHMRC	Level of evidence according to the NHMRC
Garcia [31]	2009	range 5-18	9H/9HC	NR	NR	NR	2	Before and after each session (8 measurements)	non-randomised experimental trial	III-2
Hill [37]	2009	39.4 (95% CI: 33.7-45.1) range: NR	20H	18 A; 1 B; 1 A and von willebrand factor. 14 severe, 4 moderate and 2 mild	NR	NR; neurological comorbidities that would increase risk of falling were an explicit exclusion criteria	1	Before and after 4 months of training	case series	IV
Vallejo [35]	2009	32.3 (SD 1.5) range: NR	13H	12 severe A; 1 moderate A	9 on-demand; 4 prophy-lactic treatment.	all patients serologically positive for hepatitis C virus and 77% presented the Immunodeficiency disease	1	Before and after 9 weeks of training	case series	IV

Table 1: Study design and subject characteristics (continued)

Study	Year	Age (years)	N	Type and severity	Treatment	Comorbidities	Number of groups	Time and number of measurements	Design according to the NHMRC	Level of evidence according to the NHMRC
Mulvany [38]	2010	range 7-57	30H	26 severe; 3 moderate; 1 mild	some were on a regimen of prophylactic factor replacement; severe patients were given a prophylactic dose of factor prior to exercise	12 patients had comorbidities such as HIV/AIDS, hepatitis, diabetes, fibromyalgia, neorofibromatosis, osteopenia, osteogenesis imperfecta, or cancer.	1	Before and after 6 weeks of training	case series	IV

Legend: H, haemophilia patient; HC, healthy control; AHC, active healthy control; PHC, passive healthy control; NR, not reported; NHMRC, National Health and Medical Research Council

Table 2: Methodological quality of included studies

	Quality criteria*									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	
Study										**Total score (0-10)**
Greene [34]	1	0	1	0	0	0	0	1	0	3
Querol [30]	1	0	1	0	0	0	0	1	0	3
Vallejo [35]	1	0	1	0	0	0	0	1	0	3
Gomis [29]	1	0	1	0	0	0	0	1	0	3
Hilberg [32]	1	0	0	0	0	0	0	1	0	2
Hill [37]	0	0	0	0	0	0	0	1	1	2
Mulvany [38]	0	0	1	0	0	0	0	1	0	2
Garcia [31]	0	0	0	0	0	0	0	1	0	1
Gurcay [36]	0	0	0	0	0	0	0	1	0	1
Median (IQR)										2 (1.5-3)

Legend: IQR, Interquarile range. *Quality criteria 1. Selection of the patients intervention group, 2. Selection of the control group, 3. Reproducibility of the training program, 4. Registration of training sessions participation, 5. Assessment of outcome, 6. Follow-up, measurement performed and was long enough, 7. Adequacy of follow-up, 8. Test method used for measurement physical fitness, 9. Assessment of quality of life and/or functional capacity. (See appendix A for detailed description of criteria). If a study meets a criterion it is scored as "1", otherwise it is scored as "0".

Intervention characteristics and effects

Detailed characteristics of the exercise interventions are shown in Table 3. Three studies mainly focussed on promotion of muscular strength [29,30,34] and one study mainly focused on flexibility [31]. The remaining studies were aimed at simultaneously improving multiple aspects of health-related physical fitness.

Two interventions were water-based (aquatic training) [31,35] whereas the other studies were land-based. Programme length varied from 4 to 24 weeks. Training frequency ranged from 1 to 7 days per week and duration of the sessions ranged from 15 to 120 minutes. Details on intensity of exercise were reported in two studies only [35,38]. For strength training, Vallejo et al. [35] used a perceived exertion of 2 to 7 (out of a maximum score of 10) and Mulvany et al. [38] chose 40-70% of the 1 repetition maximum. For aerobic exercises Vallejo et al. [35] chose 50 to 75% of the maximal heart rate, whereas Mulvany et al. [38] used 50-70% of the maximal heart rate. Supervision was provided by a physical therapist

during the entire programme in one study [38], and part of the intervention in two other studies [36,37]. In one study patients performed the exercises unsupervised [34] and the remaining studies did not report details about supervision.

The included exercise interventions reported many positive effects. We will summarize the main findings here according to the ICF levels. A more detailed description of the effects of the exercise interventions is presented in Table 4. On the level of "body functions and structures", five studies reported improved muscle strength after exercise intervention [29,30,32,34,38], whereas muscle strength remained unchanged after the home-based training programme of Hill et al. [37]. Positive effects of exercise intervention on joint range of motion were reported in the studies of Gurcay et al. [36] and Hill et al. [37]. The study of Garcia et al. [31] showed gains in some joints only. The home-based resistance training of Greene [34] showed no effect on ROM, however this study was not specifically aimed at improving ROM but rather on improving muscle strength. The study of Hill et al. showed no effects of home-based exercise on balance [37] and Hilberg et al. reported improved performance on most but not all tests of proprioception after intervention [32].

On the level of "activity", Gurcay et al. found that a clinical rehabilitation programme with additional home exercises decreased the level of disability [36], Hill et al. reported unaltered activity profile as a result of their home-based training programme [37] and the interventions of Vallejo et al. [35] and Mulvany et al. [38] resulted in improved functional walking performance. None of the included studies evaluated the effectiveness of exercise intervention on the level of "participation".
Complications were reported in two studies: Greene et al. [34] reported that some patients with bad joint status reported peripattellar pain during exercises, and Gurcay et al. [36] reported 2 patients developing a joint haemorrhage during the intervention. One study did not report details about safety [31] and the five remaining studies report the exercise programme to be fully safe.

Table 3: Description of exercise intervention

Study	Type and content of exercise programme	Length (weeks)	Frequency (per week)	Intensity	Duration (min)	Supervision	Individual/group
Greene [34]	Home-based modified isokinetic resistance training without additional weights. Crossing the legs and contracting knee extensors and knee flexors of contra lateral legs at the same time	24	7	self selected	15	None	Individual
Hilberg [32]	A specialized physical training programme consisting of strength, flexibility and proprioception exercises.	24	2	NR	120	NR	Individual
Querol [30]	Electrical stimulation of the quadriceps femoris of the left leg. Participants were encouraged to increase the intensity every session.	6	3	self selected	30	NR	Individual

Table 3: Description of exercise intervention (continued)

Study	Type and content of exerciseprogramme	Length (weeks)	Frequency (per week)	Intensity	Duration (min)	Supervision	Individual/group
Gurcay [36]	Clinical rehabilitation programme consisted of resistance, proprioception and flexibility. Additionally, home exercises were prescribed which consisted of isometric, isotonic, strengthening and proprioception exercises.	4	5	NR	in clinic: 60	PT in the clinic. No supervision during home exercises.	Individual
Gomis [29]	Electrical stimulation of the biceps brachii of both arms . Participants were encouraged to increase the intensity every session.	8	3	self selected	35	NR	Individual
Garcia [31]	Aqua training programme consisting of four subsequent parts with a main emphasis on gaining flexibility.	8	1	NR	30	NR	Group
Hill [37]	Home based training programme aimed at identified balance and mobility problems. The programme consisted of six to eight exercises, including balance exercises, lower limb strength exercises and a walking programme.	16	5-7	NR	NR	After initial assessment by a PT the subjects trained unsupervised at home	Individual

Table 3: Description of exercise intervention (continued)

Study	Type and content of exercise programme	Length (weeks)	Frequency (per week)	Intensity	Duration (min)	Supervision	Individual/group
Vallejo [35]	Aqua training consisting of exercises for muscular endurance, muscular strength and aerobic capacity.	9	3	Muscle endurance and strength exercises: ratings of perceived exertion increased from 2-7 (out of 10). For the aerobic exercises %of HRmax was used. This increased from 50-75% during the programme**	60 (10 minutes warm-up; 20 minutes muscle strength and endurance; 20 minutes aerobic exercise; 10 minutes relaxation)	NR	Group
Mulvany [38]	Strength, flexibility and aerobic exercises.	6	2	Intensity of strength training was tailored to joint status: worst joints 40-70% of 1RM; mild to moderate impairment 50-75% of 1RM; minimally affected joints 60-75% of 1RM. Aerobic exercise started at 50% of HRmax and progressed by 5-10 % per week up to70%***	Total programme: NR; Aerobic exercise: up to 20 minutes;	Fitness instructor	Individual

Legend: NR, not reported; 1RM, one repetition maximum; HRmax, maximal heart rate; PT, physiotherapist; * Results estimated from graphs. ** A detailed overview of exercise intervention characteristics is reported in the article of Vallejo et al. [35]. *** A detailed description of exercise intervention characteristics and progression is described in the article of Mulvany et al. [38].

Table 4. Safety, compliance and effects of exercise interventions

			Results according to ICF level			
Study	**Safety**	**Compliance**	**Body stucture and functions**	**Activity**	**Participation**	**Other**
Greene [34]	No increase in haemarthroses during exercise training. Some patients with bad joint status experienced peripattellar pain during exercise.	For 24 knees were trained <60 days; 20 knees were trained for 60-100 days; 20 knees were trained for >100 days.	Increased strength of knee extensors (+22%) and knee flexors (+25%) for total group. Patients with worst joint status not improved their knee extensor strength. No significant strength gains in children 7-12 years (n=4). Increased thigh girth (+1cm) in 32 thighs; no change in 28 thighs and decreased (? 1 cm) in 4 girths. No change in passive ROM. No change in arthropathy severity.	-	-	-
Hilberg [32]	No bleeding occurred due to the training programme	One H subject stopped the training programme because of a surgical intervention not due to the programme. Another H subject and three AC subjects stopped training because of personal reasons.	Muscle strength: Maximal isometric muscular strength in the legs, bilaterally measured by knee extensor (and leg press) was increased significantly by 34% (29%) after training in the H and by 20% (28%) in the AC groups while remaining unchanged in the PC group. Proprioception: The performance in one-leg-stand tests after training was significantly increased in the H and AC groups. A significant improvement of angle reproduction of 20 and 40 (but not in 60 an 100 degree angles) in the H compared with the PC groups was seen in the tests. Quantitative sensory testing by the tuning fork showed a significant increase in performance of both H and AC groups.	-	-	-

Table 4. Safety, compliance and effects of exercise interventions (continued)

			Results according to ICF level			
Study	**Safety**	**Compliance**	**Body stucture and functions**	**Activity**	**Participation**	**Other**
Querol [30]	No bleeding occurred due to the training programme	NR	Muscle strength of the stimulated and non-stimulated leg of patients improved significantly by 13.8% and 17.1% respectively. Electromyography values were unchanged and significant hypertrophy was observed in the stimulated leg of patients (+24.3%). No differences in these variables were observed in healthy controls.	-	-	-
Gurcay [36]	2 patients developed new haemarthroses during training programme, and factor replacement therapy was applied by the haematologist.	NR	Gilbert score improved 40%; disability score improved 65%; pain score improved 90%; range of motion improved in all joints.*	Disability decreased significantly by 65%.*	-	-
Gomis [29]	No bleeding occurred due to the training programme	6 patients (40%) left the study for personal reasons	Diameter of the biceps brachii increased 15.9% in the patient group. Muscle strength increased 4.6% in patients, and emg activity increased significantly with 37.6% in patients. No changes in these parameters were noted in the healthy control group.	-	-	-
Garcia [31]	NR	NR	Indications for mobility gain in elbow, knee and ankle joints especially for the first few training sessions. Mobility gains were less in subsequent training sessions. (questionable use of statistics). Healthy controls showed higher pre and post gains in mobility than haemophilia patients for the knees and left ankles.	-	-	-

Table 4. Safety, compliance and effects of exercise interventions (continued)

Study	Safety	Compliance	Results according to ICF level			
			Body stucture and functions	Activity	Participation	Other
Hill [37]	No participant ceased the exercise programme because of joint complications associated with the exercise programme and there were no accidents or falls while performing the home exercise programme	12 out of 20 participants completed the exercise programme and attended the 4 month review assessment (40% drop out). Reasons for not completing the programme include lack of time, other illnesses or co-morbidities that affected ability to participate. Lack of motivation or interest in the programme and not believing it was going to be of benefit	No significant differences were measured pre and post test for the following parameters: Static balance, dynamic bilateral stance balance, dynamic single limb balance, gait and mobility and Leg muscle strength. The level of pain was not different between pre and post-test measures.	Human activity profile was unaltered pre and post exercise	-	Fear of falling was similar pre and post exercise
Vallejo [35]	NR	4 patients (31%) abandoned the aquatic training programme for personal reasons	Significant increase in absolute and relative aerobic capacity (+52% and 70% respectively). A significant lower respiratory quotient was measured during the post-test. There was no significant difference in peak heart rate pre and post-test.	The distance covered during a 12 minute walk test was significantly increased by 15%.	-	-

Table 4. Safety, compliance and effects of exercise interventions (continued)

Study	Safety	Compliance	Results according to ICF level			
			Body stucture and functions	**Activity**	**Participation**	**Other**
Mulvany [38]	Non of the participants reported any adverse reactions from the exercise program	Thirteen participants (39%) did not complete the programme due to transportation problems, illnesses, or scheduling difficulty.	Range of motion improved significantly for all measured joints (knees, ankles, and elbows) with ES ranging from 0.17 (elbow supination) to 0.7 (ankle plantar flexion) ; muscle strength improved significantly in all muscle groups tested (hips, knees, and elbows) with ES ranging from 0.08 (elbow flexion) to 1.66 (hip extension); joint circumference were significantly different for the elbows with effect sizes of -0.12 to 0.2. No differences in joint circumference was reported for the knees;	the distance covered during a 6 minute walk test was significantly increased by 25%.	-	-

Outcome measures used and best-evidence synthesis

Table 5 shows all outcome measures that were used to evaluate the status of the patient before and after an exercise intervention. A more detailed description of outcome measures used are shown in appendix B. All studies reported one or more aspects of "body functions and structures", four studies reported on an aspect of "activity" and no studies reported on aspects of "participation". One study reported on an aspect of psychosocial functioning [37]. Because no study exceeded the threshold value of 5 (to be ranked as high quality study), all outcome measures were assigned the status of a poor evidence base. For example: muscle strength was the most commonly reported outcome measure and was measured in six studies. Although the effects seemed consistently positive (5 studies reported improved muscle strength, and one study reported no change in muscle strength), the low quality of the studies (Table 2) resulted in a poor body of evidence for this measure.

Body functions and structures

All studies reported included at least one outcome measure on the level of body functions and structures. Of 25 reported outcomes on the level of body functions, nearly half (n=11; 44%) focused on muscle structure or function. Specifically the following aspects were measured: muscle strength (n=6), muscle diameter (n=2), muscle electromyography (n=2) and muscle circumference (n=1). Joint function or structure was also reported frequently (n=7; 28%). Specific aspects that were measured are: range of motion (n=4), arthropathy (n=1), clinical joint score (n=1) and joint circumference (n=1). Aspects of balance/proprioception were also measured but less frequent (n=4; 16%). Specific aspects measured in this area were: static proprioception, dynamic proprioception, local proprioception and balance (all reported once). Other outcome measures reported are perceived pain and aerobic fitness (both reported once). Again, a detailed description of the outcome measures is presented in appendix B.

Activity

Four studies measured outcomes on the level of activity. In two studies a subjective activity measure (i.e. self report) was used: the Human activity profile questionnaire [37] and the Juvenile Arthritis Functional Assessment Report for Children (JAFAR-C) [36]. In four studies objective measures of activity were used: the timed sit to stand test [37], a laboratory gait test (Neurocom Balance Master

long plate) [37], the 6-minute walk test [38] and the 12-minute walk/running test (Cooper test) [35].

Participation

None of the studies included evaluated outcome on the level of participation

Other

One study included an outcome measure fear of falling with a questionnaire (the modified falls efficacy scale) [37].

Table 5: Outcome measures used according to ICF levels and best evidence synthesis

		Effect post-training				
Outcome measure	**Number of studies assessed**	**+ (nr of studies)**	**= (nr of studies)**	**- (nr of studies)**	**+/- (nr of studies)**	**Body of evidence**
Body functions and structures						
Arthropathy (x-ray)	1	0	1	0	0	Poor
Clinical joint score (Gilbert score)	1	1 [36]	0	0	0	Poor
Joint circumference	1	0	0	0	1**[38]	Poor
Joint range of motion	4	2 [36,38]	1 [34]	0	1*** [31]	Poor
Muscle strength	6	5 [29,30,32, 34,38]	1 [37]	0	0	Poor
Muscle circumference	1	0	0	0	1* [34]	Poor
Muscle diameter	2	2 [29,30]	0	0	0	Poor
Muscle electromyography	2	1 [29]	1 [30]	0	0	Poor
Static proprioception	1	1 [32]	0	0	0	Poor
Dynamic proprioception	1	0	0	0	1**** [32]	Poor
Local proprioception	1	1 [32]	0	0	0	Poor
Balance	1	0	1 [37]	0	0	Poor
Perceived pain	2	1 [36]	1 [37]	0	0	Poor
Aerobic capacity	1	1 [35]	0	0	0	Poor

Table 5: Outcome measures used according to ICF levels and best evidence synthesis (continued)

		Effect post-training				
Outcome measure	**Number of studies assessed**	**+ (nr of studies)**	**= (nr of studies)**	**- (nr of studies)**	**+/- (nr of studies)**	**Body of evidence**
Activity						
Gait	1	0	1 [37]	0	0	Poor
Human activity profile						
Questionnaire	1	0	1 [37]	0	0	Poor
Timed sit to stand test	1	0	1 [37]	0	0	Poor
Functional ability by						
JAFAR-C questionnaire	1	1 [36]	0	0	0	Poor
Functional walking ability	2	2 [35,38]	0	0	0	Poor
Participation						
-						
Other						
Fear of falling by falls						
efficacy questionnaire	1	0	1 [37]	0	0	Poor

Legend: +, improvement; =, no effect; -, deterioration; +/-, inconclusive.
* Increased thigh girth (+1cm) in 32 thighs; no change in 28 thighs and decreased (≥ 1 cm) in 4 girths. ** joint circumference were significantly different for the elbows with effect sizes of -0.12 to 0.2. No differences in joint circumference was reported for the knees. *** Indications for mobility gain in elbow, knee and ankle joints especially for the first few training sessions. Mobility gains were less in subsequent training sessions (questionable use of statistics). **** A significant improvement of angle reproduction of 20 and 40 (but not in 60 an 100 degree angles) in the H compared with the PC groups was seen in the tests.

DISCUSSION

The aims of this review were to review the literature regarding exercise interventions in patients with haemophilia, to provide an overview of the intervention characteristics, the methodological quality and the effectiveness of these interventions and to review the types of outcome measures used in exercise interventions for haemophilia patients.

Intervention characteristics

Exercise interventions in haemophilia patients may have several aims. Depending on type of treatment the focus of exercise interventions is more on improvement of functional outcome, physical fitness and quality of life. For example in patients

with bad joint status exercise may be more directed towards restoring range of motion, muscle strength and functional ability. On the other hand, in the relatively unaffected young patients who are on prophylaxis the focus may increasingly be on prevention of bleeding episodes and cardiovascular disease. Although we observed many positive effects of prescribed exercise intervention, such as increased muscle strength, increased joint range of motion and improved functional ability, the level of evidence for the effectiveness of the exercise interventions for patients with haemophilia was low. Summarizing the major shortcomings in the studies that have been reviewed, these are: 1] lack of methodological quality, 2] lack of specificity of the training goals and 3] lack of physiological criteria to generate a training response. This underlines the need for methodologists as well as exercise physiologists aboard of research teams.

Lack of methodological quality mainly comes down on designing proper prospective, (randomized) controlled trials, preferably with a long wash out period to be able to fully appreciate the impact of the training intervention. As in many countries haemophilia care is provided by centralized comprehensive care units, this should be a realistic aim. Nation wide networks of these centres should enable researchers to draw enough statistical power to secure valid and meaningful outcome. Beyond that international consortia of researchers should pull the resources and this may even result in robust cross cultural results.

A major shortcoming of many studies was the lack of well defined training goals. Exercise training is specific (e.g. “you gain what you train”), this refers to the training law that the greatest achievements are reached in the function or activity that is actually trained. Consequently, the best fitting outcome measure in relation to that training goal should be chosen. This paradigm should be utilized more frequently in the design of intervention studies in haemophilia research.

The third shortcoming in many studies is the lack of properly designed training programmes that adhere to basic principles of exercise physiology. To gain from an exercise intervention the sessions have to systematically “overload” the body system so that it is forced to recover from this exercise induced damage or fatigue. Ideally, this will lead to adaptation processes and the recovery of the body system, which will result in a higher physical fitness level then before the training session. The overload principle is a key component of training and can be achieved by manipulating several aspects of the training. Aspects such as frequency, intensity, time and type of exercise (referred to as F.I.T.T. factors) define the training dose and should progress over time because the person is adapting physically to the increased demands of the training load. The most important factor for eliciting a

training response is intensity of training. A training session (aerobic exercise or resistance training) should exceed a minimum threshold value for intensity to result in a training response.

A recent position stand of the American College of Sports Medicine (ACSM) describes the recommendations for the quantity and quality of exercise for developing cardiorespiratory, musculoskeletal, and neuromotor fitness [39]. With regard to cardiorespiratory fitness, the ACSM recommends performing either moderate-intensity (i.e. 64-76% of maximal heart rate) cardiorespiratory exercise training 5 days per week for a total of ≥150 min per week, vigorous-intensity (77-95% of maximal heart rate) cardiorespiratory exercise training for ≥20 min per day on ≥3 days per week or a combination of moderate and vigorous exercise to achieve a total energy expenditure of ≥500-1000 MET/min/week [39].

With regard to resistance training, exercising major muscle groups, 2 to 3 times per week, 2-4 sets of 8-12 repetitions using a resistance equivalent to 60-80% of the individual 1 repetition maximal (1-RM) has shown to be effective for inducing hypertrophy and improving strength. For novice through intermediate strength trainers a load of 60-70% of the 1RM is recommended, while experienced exercisers may work at ≥80% of the 1RM. The selected resistance should permit the completion of 8-12 repetitions per set or the number needed to induce muscle fatigue but not exhaustion. Middle aged and older persons staringstarting exercise may use 10-15 repetitions per set. In older, very deconditioned or frail individuals a resistance training regimen may begin with lower resistance, perhaps 40-50% of 1RM (i.e.. very light to light intensity). After achieving an acceptable level of muscular conditioning, older and frail persons can increase the resistance and perform the exercises as detailed above [39]. Future studies of exercise interventions in patients with haemophilia should adopt above recommendations and report on its success in this specific patient population.

Of course, safety of the exercise programme should be a main objective and we recommend the use of proper equipment and supervision of well-educated fitness professionals. Exercise programs reviewed in this paper reported very few complications, especially when patients were treated with prophylaxis during the training programme. Safety should however not lead to inadequate exercise stimuli that are of little benefit for the patients. On the contrary however, we recognize the fact that in highly sedentary patients with poor physical fitness, training sessions that not meet the recommended volume and intensity as stated above could still be beneficial to their health, especially by reducing the risk of cardiovascular disease and premature mortality [40-42]. However to really make substantial gains in

physical fitness volume and intensity must be raised to minimum levels and should progress throughout the training programme.

Uniformity

Patients with haemophilia show positive responses on different exercise interventions, which support the notion that it may be feasible to design effective exercise interventions that improve body functions or physical activities in patients with haemophilia. However, to enhance meaningful comparison among studies and pooling of study results, much more uniformity is needed with regard to type of interventions, intensity of exercise interventions and type of outcome measures. There are a few responsive outcome measures that are able to substantiate gains from exercise programmes in patients with haemophilia, and there are new outcome measures that not have been utilized in intervention studies. Functional or activity based outcome measures seem to increasingly being included in exercise intervention studies in haemophilia. Four studies published in the past three years have included a measure of functional activity [31,35,37,38]. In our opinion this is a positive and much needed paradigm change.

Recently many disease specific instruments for patients with haemophilia have been developed and tested [43-52]. If haemophilia researchers around the globe could reach a consensus on selecting outcome measures for exercise training in patients with haemophilia, then this will greatly help to build an evidence base regarding the effectiveness of exercise interventions in patients with haemophilia. An ICF based 'core setset' of outcome measures would be very useful for the haemophilia community. De Kleijn et al. have proposed a core set of outcome measures based on literature review [53]. In the field of (paediatric) rheumatology, for instance, the OMERACT and PRINTO initiatives have proven to be successful ways to selecting the best possible outcome measures (in terms of psychometrics and feasibility) based on literature and expert opinions in an iterative manner [54,55]. This procedure might serve as a good example for the haemophilia community.

Limitations

This review has some limitations. Firstly, our inclusion criteria were quite liberal with regard to the types of studies being included. Within the field of haemophilia research on this topic is scarce leaving few other options. A more mature field of research would enable more specific inclusion criteria and more focussed research questions (e.g the effectiveness of lower extremity resistance training on functional

walking ability). This review should therefore be considered as a motivation for clinicians and researchers to reconsider the approaches to exercise trials in haemophilia.

A second limitation is the grouping of outcome measures in the best evidence synthesis as shown in Table 5. For example, muscle strength was measured using different methods at different muscle sites but was shown as one outcome measure. However we do find this approach valuable because it gives a rough insight into the effectiveness of the exercise training interventions in haemophilia. When the research field progresses outcome measures could eventually be grouped into more homogeneous sub-groups. For example, muscle strength could be subdivided into upper and lower extremity strength, or even into specific muscles and different forms of muscle strength (isometric muscle strength, dynamic muscle strength, isokinetic muscle strength).

Conclusions

Although we observed many positive effects of prescribed exercise intervention, the methodological quality and level of evidence of the included studies was low. No single RCT could be included. However, evaluating currently available data, it appears that exercise training interventions for patients with haemophilia are generally safe and might result in improved physical functioning, however the current evidence base for the effectiveness of all exercise interventions is poor. The outcome measures used in most studies often focused on the ICF level "body functions and structures" and to a lesser extent on the level of "activities". The field is in dire need of large, well-controlled trials investigating the effects of exercise training as an intervention in patients with haemophilia and in a well defined set of outcome measures that are fit for their job.

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Appendix A: Methodological quality assessment

Modified Newcastle – Ottawa Quality assessment scale cohort studies

1. Selection of the patient intervention group:
patients were from similar diagnose group (homogeneous) (+)
patients scored into functional groups (+)
patient group was heterogeneous (-)
no description of the cohort (-)

2. Selection of the control group
control group were patients (+)
two control groups; patients and healthy subjects (+)
control group were healthy subjects (-)
no control group (-)

3. Reproducibility of the training program
detailed description providing; duration program, frequency, duration session, trainings intensity (+)
brief description (-)
no description (-)

4. Registration of training sessions participation
reported and sufficient with >75% of training sessions completed (+)
reported and not sufficient with <75% of training sessions completed (-)
not reported (-)

5. Assessment of outcome
independent blind assessment (+)
record linkage (+)
self report (-)
no description (-)

6. Follow-up measurement performed and was long enough.
follow-up was >3months after ending the training program (+)
follow-up was <3months after ending the training program (-)
no follow-up (-)

7. Adequacy of follow-up
Complete follow-up (all subjects completed) (+)
< 15% of subjects lost during follow-up, unlikely to introduce bias, and description provided for those lost (+)
> 15% of subjects lost during follow-up and no description provided for those lost (-)
No statement (-)

8. Test method used for measurement physical fitness
Valid test method used (+)
brief description of used method (-)
no description of method (-)

9. Assessment of quality of life and/or functional capacity
Validated questionnaire (+)
Briefly described, no questionnaire used (-)
No statement (-)

Appendix B: Outcome measures used according to ICF level

	Body functions and structures	Activity	Partici pation	Other
Greene [34]	Torque of quadriceps on Cybex machine at 30º/sec; Passive ROM knee (method NR); Thigh girth; degree of arthropathy (X-ray); no. of haemarthroses	-	-	-
Hilberg [32]	Muscle strength was measured isometrically in two positions (leg press and leg extension) with knees bent in a 70 degree angle on a strength training apparatus (Schell, Pautenhausen, Germay). Proprioception was measured by four tests: 1) one legged stance on two surfaces (hard and soft ground) and with two visual conditions (eyes open and eyes closed). 2) The postural resettling time on a posturomed platform (Posturomed, Haider bioswing, Pullenreuth, Germany) which is displaced 2 cm in a mediolateral direction. The mean of 5 tests was taken 3) the reproduction of several knee joint angles (20, 40,60 and 100 degrees knee flexion in random order) which were first demonstrated passively. Knee angles were measured by an electric goniometer and hearing and sight of the participants were blocked. 4) Tuning fork test; a tuning fork 64Hz is placed on the corpus of the os metacarpale II and the caput of the os metatarsale I and the subject has to report at what amplification he still feels the vibration. The amplification of the vibration can be set at 0-8 (artbitrary units).	-	-	-
Querol [30]	Muscle strength measured by maximum voluntary contraction (isometric) with hips and knees fixed and knees in a 90 degree angel. Best of measure was used. Muscle activiation was measured by surface EMG and muscle diameter was measured by computerized tomography.	-	-	-
Gurcay [36]	Clinical score of the joints by the Gilbert scoring system. Pain by ? (score range 0-3). Range of motion was most probably measured by standard goniometry. This this was not mentioned in the methods section results show outcome in degrees, which implies the use of standard goniometry.	Functioanl ability was measured by the JAFAR-C	-	-

Outcome measures used according to ICF level (continued)

	Body functions and structures	Activity	Participation	Other
Gomis [29]	cross-sectional are of the biceps was measured by compuerized axial tomography. Muscle strength was measured by maximal voluntary isometric contraction (MVIC). Elektromyographica activity was measured by surface emg with Ag/AgCl bipolar elektrodes during the MVIC.	-	-	-
*Garcia [31]	Range of motion was measured by goniometry.	-	-	-
Hill [37]	Static balance was measured by The neurocom balance master long plate , dynamic bilateral stance balance was measured by the neurocom and by functional reach test, dynamic single limb balance was measured by the step test (steps per 15s), gait and mobility was measured by measures of the neurocom (gat speed, gait step length, step width, step quick turn sway) and Leg muscle strength by the timed up and go test and by an isometric strength test (maximal voluntary contraction) of the quadriceps by strain gauge (this test is part of the physical profile assessment Lord et al. Phys ther 2003 83 (237-52). Pain was measured by a 10 cm Visual analogue scale.	The activity level was measured by Human activity Profile questionnaire	-	Fear of falling/ falls efficacy was measured by the Modified Falls Efficacy Scale (MFES)
Vallejo [35]	Aerobic capacity was measured by the oxygen uptake during the cooper 12 minute walk/run test. Also significant weight loss during the trial from 81.3 to 72.4 (calculated from data)	Functional walking ability was measured by the total distance covered during the 12 minute cooper cooper 12 minute walk/run test	-	-
Mulvany [38]	ROM was measured by goniometry; Muscle strength was measured isometrically with a handheld dynamometer; circumference of the joints was measured by a measurement tape at marked landmarks.	Functional walking ability was measured by the total distance covered during the 6 minute walk test.	-	-

Chapter 7

Protected by nature? Effects of strenuous physical exercise on VIII activity in moderate and mild haemophilia A patients: a pilot study

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SUMMARY

Increase of factor VIII activity (FVIII) after physical exercise has been reported in healthy subjects and small scale studies in patients with coagulopathies. We studied whether moderate and mild haemophilia A patients are able to increase their endogenous FVIII activity levels by physical activity.

We studied changes in FVIII activity levels after high intensity exercise in 15 haemophilia A patients, 20-39 years, 8 with moderate, 7 with mild haemophilia. Patients cycled until volitional exhaustion, blood samples were drawn before and 10 minutes after the exercise test.

FVIII activity increased 2.5 times (IQR 1.2-4.0 times), for both severities. Absolute increases were markedly different: median 7 IU/dl (range 3-9 IU/dl) in patients with moderate, compared to 15 IU/dl (range 6-62 IU/dl) in mild haemophilia patients. VWF and VWFpp increased independently of severity; median 50% (IQR 30-79%) and median 165% (IQR 130-244%) respectively, reflecting acute release of VWF.

These observations may be used to promote high intensity activities before participating in sports for moderate and mild haemophilia A patients, to reduce bleeding risk. Further studies are warranted to fully appreciate the clinical significance of exercise on different levels of intensity in patients with mild and moderate haemophilia A.

INTRODUCTION

Physical exercise is an essential part of a healthy lifestyle, as it reduces risk of coronary disease [1] and diabetes [2], and promotes well-being [3,4]. Yet, sports participation is lower in patients with haemophilia than in healthy peers [5,6]. Haemophilia A patients lack clotting factor VIII (FVIII), resulting in a high risk of joint bleeds. Severe haemophilia patients (FVIII <1IU/dl, or <1% of normal levels) suffer from spontaneous joint bleeds, which untreated will lead to crippling haemophilic arthropathy [7]. Patients with moderate (FVIII 1-5 IU/dl) or mild (FVIII 6-30 IU/dl) haemophilia generally only bleed after trauma or overexertion.
The perceived bleeding risk has hampered participation in sports in many haemophilia patients [5]. Historically, these patients were recommended low impact sports such as swimming [6]. Fortunately, treatment has been intensified and currently more than half of haemophilia patients in the Netherlands actually participate in a variety of sports, even contact sports such as soccer [8].

The effect of exercise on blood haemostasis has been studied extensively in healthy subjects. Several studies have reported that acute bouts of exercise of varied intensity and duration induced a significant increase in FVIII activity [9-13]. In healthy populations, increase in FVIII activity and FVIII antigen were positively associated with exercise intensity [14]. Unfortunately there are only few studies in which the effect of exercise on factor VIII production have been assessed in patients with haemophilia [15-17]. These studies have some limitations that warrant further study. The study of Koch et al. [15] shows an increase of factor VIII activity in one moderate and three mild patients with factor levels ranging from 14.5 to 17.3%. However an increase was not seen in seven severe patients. This small number of patients limits generalization of these findings. The study of Roya et al. [16] included patients with a relatively high clotting factor activity (average FVII activity of 12%) and used an exercise protocol that was very time consuming (mean exercise time of 37 minutes) [18].

The aim of the present study is to examine the effect of standardized exercise on FVIII levels in mild and moderate haemophilia A patients, which may lead to less reserve towards sports or other strenuous physical activities in these patients.

METHODS

In this pilot study, fifteen consecutive non-severe haemophilia A patients with FVIII activity levels of 1-15 IU/dl volunteered to participate. After signing informed consent, coagulation parameters were measured before and after a standardised incremental exercise test. Patients were considered able to complete the test if they did not have any disability preventing them from cycling or strenuous physical activity. This study was approved by the medical ethical committee of the Utrecht Medical Centre, Utrecht, the Netherlands.

Exercise testing procedure

Patients performed a graded exercise test on an electronically braked cycle ergometer (Ergoline 9000, Germany). Subjects started with one minute of unloaded cycling after which the load was increased with 25W every minute. Pedalling frequency was 60-80 revolutions/min. This protocol was continued until the patient stopped because of volitional exhaustion, despite strong verbal encouragement of the investigator. During the test heart rate (HR), oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured with a calibrated portable breath-by-breath system (metamax 3B, Cortex biophysik, Germany). Respiratory Exchange Ratio (RER) was calculated as VCO_2/VO_2. A test was rated as maximal when at least 2 out of 3 of the following criteria were met:1) plateau in VO_2, 2) peak RER > 1.0, and 3) maximal HR within 10 beats of age predicted maximum for age (220 minus age). Peak HR and peak work rate were defined as the highest value measure (10 second intervals). Absolute peak oxygen uptake (VO_2peak) was defined by the average value over the last 30 seconds of the maximal exercise test. Relative VO_2peak (VO_2peak/kg) was calculated as absolute VO_2peak divided by weight. Peak values for oxygen uptake were compared to established reference values [19].

Blood collection procedure and laboratory assays

Blood samples were collected by a research nurse before and ten minutes after the maximal exercise test.. Ten minutes after maximal exercise was considered to be appropriate to measure the response of factor VIII and was based on previous studies in healthy subjects as well as patients with haemophilia [16,17,20]. All punctures were performed atraumatically (only blood immediately successful punctures was used) in the cubital vein. For each sample, 4.5 mL was collected in a citrate tube. Blood samples were spinned for 15 minutes at 2000*g and stored at -

40°C until analysis. All samples were analyzed in one batch (to avoid inter-assay differences) at the certified haematology laboratory of the UMC Utrecht, the Netherlands. Plasma levels of FVIII activity, von Willebrand factor (VWF) and von Willebrand propeptide (VWFpp) were assessed in all samples. FVIII activity was assessed using the one-stage assay on a STA-Rack evolution [21]. VWF antigen was measured by enzyme-linked immunoabsorbent assay (ELISA) using a polyclonal antibody against human VWF for capture and detection [22,23]. The concentrations of VWFpp were determined with a standard ELISA on a Tecan Freedom EVO pipetting robot [24].

Statistics

Data analysis was performed using SPSS 17.0 (Chicago, Il, USA). A power calculation [25] was performed based on data of Roya et al. [16] who reported an increase of FVIII level of 3.7 IU/dl after exercise. Based on this increase, a power of 80% and a significance level of 0.05 a minimum of 12 patients was required to detect a significant difference (a two sided Wilcoxon matched pairs test). To avoid lack of statistical power, 15 patients were included in this study.

For each patient, the increase in FVIII activity was calculated. The relative increase was calculated by dividing the absolute increase in FVIII by the patient's baseline FVIII activity level. Changes in FVIII activity, VWF and VWFpp after exercise for mild and moderate haemophilia as well as the total group were compared using a Wilcoxon matched-pairs rank test. Differences in changes in FVIII activity, VWF and VWFpp after exercise between mild and moderate haemophilia were compared using a Mann-Whitney U test. In patients with mild haemophilia the changes in FVIII activity after exercise were compared to previously performed routine DDAVP response tests (i.e. increase in FVIII activity 1 hour after intravenous administration of 0.3 microgram/kg DDAVP using a Wilcoxon matched-pairs rank test.

RESULTS

Patient characteristics and test results of the exercise test are shown in Table 1. A total of 15 patients with a median age of 26.5 years (range 20-39 years) volunteered. Eight patients had moderate (FVIII 1-5 IU/dl) and 7 mild haemophilia (FVIII 6-15 IU/dl). All patients completed the exercise test without complications and all patients met at least 2 out of 3 criteria of a maximal exercise test. Median peak workload was 304 Watt (range 242-375 Watt). Median peak heart rate was

188 beats/min (range 164-199 beats/min). Median VO_2peak was 42.2 ml/kg/min (range 27.1-49.7 ml/kg/min) which was 91.0% of predicted (range 66.0-106.0%).

Table 1. Patient characteristics (n=15) and results of the incremental exercise test

	n=15
Age (years)	27 (20-39)
Moderate haemophilia (n, %)	8 (53%)
BMI	23.8 (20.3-33.5)
Time to exhaustion (min)	11 (9-15)
Peak Workload (Watt)	304 (242-375)
Peak Heart Rate (beats/min)	188 (164-199)
Peak Respiratory Exchange Ratio	1.25 (1.02-1.54)
VO_2peak (L/min)	3.40 (2.44-49.7)
VO_2peak (mL/kg/min)	42.2 (27.1-49.7)
VO_2peak (% predicted)	91.0 (66.0-106.0)

Values are median (range) or n (%)

Median baseline FVIII activity was 5 IU/dl (range 2-15 IU/dl). After the incremental exercise test, FVIII activity had increased in all patients to median 11 IU/dl (range 7-77 IU/dl), although the absolute change in FVIII activity varied widely (Fig.1). Median relative increase was similar (p=0.8) for moderate (2.4 times; IQR 1.3-4.0 times) and mild haemophilia patients (2.5 times; IQR 1.2-4.0 times). The absolute increase was higher in patients with mild haemophilia (p=0.01), resulting in higher FVIII activity levels after exercise for mild (median 21 IU/dl; IQR 19-44 IU/dl) than for moderate haemophilia patients (9 IU/dl; IQR 8-11 IU/dl).

VWF and VWFpp also increased independent of severity (p=0.3-0.6) in all patients, median 50%; IQR 30-79% and median 165%; IQR 130-244% respectively. The proportional increase in VWF was lower than in VWFpp. (Table 2) DDAVP tolerance tests were available only for patients with mild haemophilia. Relative increase after DDAVP administration was median 3.5 times (IQR 2.5-14.5 times), and was similar to the increase in FVIII activity after exercise (p=0.14).

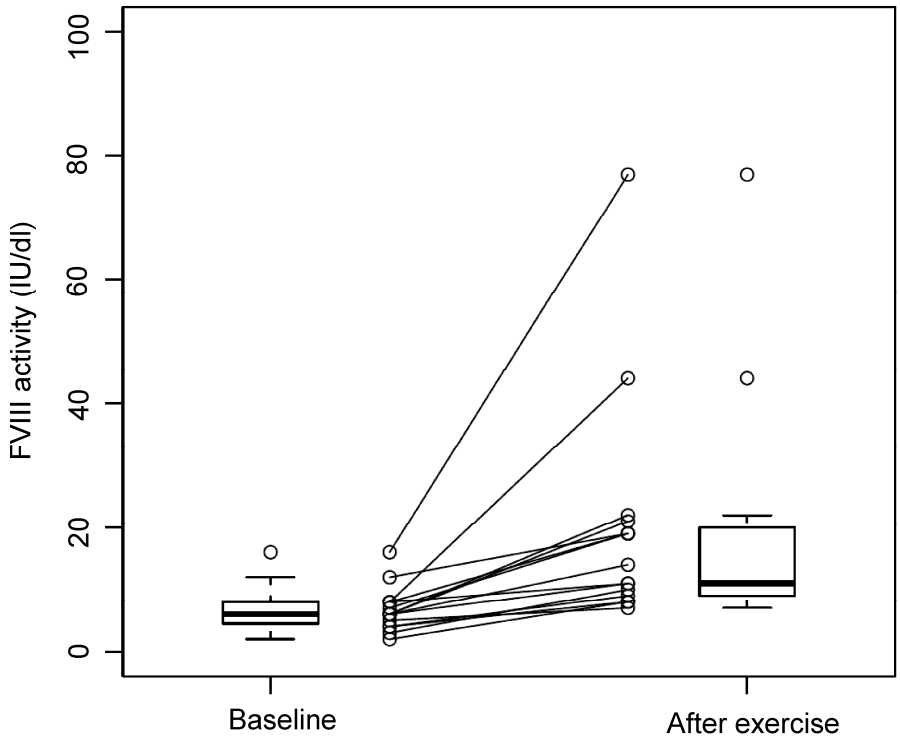

Figure 1. Baseline FVIII activity levels and after an incremental exercise test in patients (n=15) with moderate and mild haemophilia

Table 2. Increase in coagulation parameters after exercise and DDAVP administration

	Moderate (n=8)	**Mild (n=7)**	**p-value**
Absolute increase			
FVIII (IU/dl)	7 (3-9)	15 (6-62)	0.01
VWF (%)	50 (8-117)	57 (23-123)	0.42
VWFpp (%)	164 (48-346)	186 (90-350)	0.67
FVIII after DDAVP (IU/dl)	-	32 (13-87)	0.10*
Relative increase*			
FVIII	2.4 (1.8-7)	2.5 (1.9-4.5)	0.82
VWF	1.5 (1.1-2.7)	1.8 (1.2-2.9)	0.30
VWFpp	2.6 (1.5-4.1)	2.7 (2.0-4.9)	0.64
FVIII after DDAVP (IU/dl)	-	3.5 (2.2-14.5)	0.14*

Values are shown as median (range)

*increase FVIII after exercise compared to increase FVIII after DDAVP administration

DISCUSSION

The results of this study showed that patients with moderate and mild haemophilia increase their endogenous FVIII activity shortly after high intensity exercise. The relative increase of FVIII activity after exercise was independent from baseline FVIII activity level. All patients showed at least doubling of FVIII activity after exercise.

The reason for choosing patients with <15 IU/dl FVIII activity was that baseline bleeding risk is higher in these patients than in patients with >15 IU/dl [26]. These patients, who are treated on demand, have most to gain by an increase of their FVIII activity levels.

The increase in factor VIII activity levels coincide with an increase of VWF and VWFpp levels. The proportional increase was higher in VWFpp, indicating acute release of VWF from endothelial cells [27]. During exercise, as well as after DDAVP administration [28], muscular perfusion increases, VWF is washed out of the endothelial cells of the muscles and subsequently binds more FVIII.

In this pilot study it appeared that the increase in factor VIII activity after exercise was similar to after DDAVP administration in patients with mild haemophilia. In moderate haemophilia the response to DDAVP is generally very low [29]. As the increase in FVIII levels is considered insufficient for the treatment

of bleeds in moderate patients, our clinic only performs routine DDAVP response tests in mild haemophilia patients. The inclusion of patients with a low baseline FVIII activity, is expected to be one of the reasons for the limited increase in FVIII after exercise.

In addition to baseline level, other factors could impact the increase in FVIII activity, for example age and cardiorespiratory fitness. Van den Burg et al. found that factor VIII response to exercise in healthy subjects was higher for subjects that had higher cardiorespiratory fitness and were younger of age[20]. None of the patients in this pilot study participated in high-level endurance sports, such as cycling and running multiple times per week. This was reflected by the values for cardiorespiratory fitness that were in the normal range when compared to healthy *untrained* subjects. The highest VO_2peak attained was 106% of predicted, which could be considered relatively low when compared to levels attained in highly trained endurance athletes.

Although numbers were low, the increase in FVIII and VWF seem to be consistent throughout this study. There is additional evidence that submaximal exercise also results in increase in FVIII activity, albeit less pronounced. Koch et al. [15] reported grouped data on the increase of FVIII activity after an incremental exercise test in seven severe and three mild haemophilia A patients aged 8-15 years, with FVIII activity levels ranging from 14.5 to 17.3 IU/dl. As can be expected, FVIII activity did not increase in patients with severe haemophilia. Three patients with mild haemophilia showed, however, a 1.15 times increase of FVIII activity levels after submaximal exercise. The exertion in the study of Koch et al. was clearly submaximal as reflected by low mean peak workload (45W; range 37-60W) as well as the mean peak heart rate (177 bpm), which is considered quite low for children. Roya et al. [16] tested 10 patients with mild haemophilia; FVIII activity levels of 12 IU/dl (sd 3.8 IU/dl). They reported a consistent increase of FVIII activity of 1.3 times after an incremental exercise test, which was similar to that of Koch et al. Mean exercise time in the study of Roya et al. was 37.4 minutes (range 23-46), corresponding to approximately 212W (range142-267), which is almost 100W lower than in our study (mean peak workload of 304W). Unfortunately Roya et al. did not report values for peak RER or peak HR that would have defined exercise intensity more clearly. The age distribution from the study of Roya et al. [16] (24.5 years (range 17-38 years)) matched that of our study (26.5 (range 20-39)), and therefore age-related effects on VWF and FVIII [14] do not affect the comparison of the studies. In contrast with both Koch et al. [15] and Roya et al. [16] who performed submaximal exercise tests, we used a maximum

incremental exercise test, which could explain the larger increase [14]. This suggests that the intensity of the physical activity influences the increase in FVIII activity. The optmial intensity of physical activity to reduce bleeding risk remains to be studied. The increase (median 2.5 times) found in the current study is comparable to the increase found in von Willebrand patients (mean increase 1.6-2.3 times) [30] and healthy subjects [9].

The mechanism of increase in coagulation components during exercise or DDAVP is not yet fully understood, however it is suggested that it may be mediated via the ß-adrenergic receptor pathway, because ß blockade blunts this increase [31]. There have also been reports that endothelial cells could release FVIII [32,33] or even produce FVIII [32,34]. Future studies should investigate whether both DDAVP and exercise are two parts of the same mechanism or both target another system of release of additional endogenous FVIII.

Are these results reproducible in the patient's sports activities? In this study patients exercised up to a maximum workload, with heart rates of median 188 beats per minute in order to double their endogenous FVIII activity level. If patients would perform a bout of high intensity exercise (i.e. with a heart rate up to approximately 180 bpm) at the end of their warm-up routine before participating in sports, they could profit from an increase in FVIII activity and hence reduce potential bleeding complications. Although normal levels are not achieved, and the effect of a vigorous bout of exercise at the end of a warming up needs to be confirmed, the increase of FVIII activity is expected to help reduce bleeding risk during physical activity, especially in patients with moderate haemophilia. This information may be taken into consideration when counselling patients or tailoring treatment.

Results from the present study strongly suggest that sports and other strenuous activities should not be discouraged in moderate and mild haemophilia A patients, because of increased bleeding risks. Rather, these patients may benefit from their ability to raise FVIII levels during sports activities as a natural mechanism to reduce the risk of bleeding.

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Chapter 8

Summary & General Discussion

Summary

In **Chapter 1** a short introduction is given on haemophilia including an introduction on the current status of the evaluation of functional health status and the role of physical activity in patients with haemophilia. The research questions for this thesis are presented.

In **Chapter 2** a cross-sectional study is presented on the relationship between aspects of joint health and functional ability. Analyses of data of 226 children with haemophilia on intensive replacement therapy showed that in general there was little association between joint health and functional ability. Small but consistent associations were found between aspects of ankle joint health and lower extremity tasks. This finding indicates that ankle joints may require special attention during follow up of these children. This study also indicated that a haemophilia specific measure of functional ability might be useful especially for patients with good joint status. In **Chapter 3** and **4** the development of the Paediatric Haemophilia Activity List (PedHAL) is described to meet this need.

Chapter 3 describes the development and preliminary testing of the PedHAL in Dutch children with haemophilia. The structure and the main content were derived from the Haemophilia activities list (HAL). Additionally, items of other activity scales for children were considered for inclusion. Health professionals, patients, and parents evaluated this version. A pilot test in a sample of 32 Dutch children was performed to assess score distribution, construct validity and reproducibility. The analyses showed that the administration of the PedHAL was feasible and that scores were in the high end of the scale reflecting good functional status. The PedHAL correlated with joint examination scores and physical function subscale of the child health questionnaire (CHQ). The PedHAL did not correlate with mental and behavioural subscales of the CHQ. These findings support the validity of the construct of the PedHAL as a measure of functional health status. Test-retest agreement as assessed by limits of agreement was good. We concluded that the pedHAL is a promising tool, but additional testing of its psychometric properties in populations with a higher level of disability should be performed. Therefore, in **Chapter 4** we describe the psychometric testing of the paediatric haemophilia activities list (PedHAL) in a sample of Romanian children who are not on prophylaxis. Children attending the rehabilitation center of Buzias in Romania were sampled. Construct validity of the PedHAL was evaluated by concurrent testing with objective and subjective measures of physical function and functional

ability. Reproducibility was tested by a 3-day test-retest. Responsiveness to rehabilitation was assessed with the PedHAL and the Haemophilia Joint Health Score (HJHS). The median PedHAL score was nearly 20 points lower than in Dutch patients. The PedHAL correlated with Joint health, functional independence and the physical function subscale of the CHQ. The PedHAL did not correlate with the mental health and behaviour subscales of the CHQ and with a functional walking test. Test-retest reliability was good whereas test retest agreement on subsequent testing showed a considerable day-to-day variability of 17 points. A short rehabilitation program led to slightly improved HJHS scores, whereas PedHAL scores remained similar. We concluded that construct validity and test-retest reliability were good, and test-retest agreement showed some day-to-day variation. Therefore, currently the PedHAL may be more appropriate for research purposes than for individual patient monitoring in clinical practice.

In **Chapter 5** we investigated what types of physical activities Dutch patients with haemophilia engage in, how their activity level relates to national guidelines and how their cardiorespiratory fitness is compared to reference values. Furthermore we analysed the association between intensity of physical activity as well as joint health and cardiorespiratory fitness. It was found that children with haemophilia were as active as the normal population and had normal levels of cardiorespiratory fitness. Children with severe haemophilia participated more in swimming and less in competitive soccer compared to children with non-severe haemophilia. We did not find a clear relation between activity levels, joint health and cardiorespiratory fitness, which might be explained by the relative good joint health status and the questionable reliability of self reported physical activity measure used in this study.

In addition to habitual physical activity, physical exercise can also be provided in a structured manner by means of exercise interventions. In order to better understand the effects of exercise interventions on patients with haemophilia we conducted a systematic literature review in **Chapter 6**. Ultimately, nine articles matched our inclusion criteria and were included in a qualitative analysis. Overall the level of evidence and the quality of the included studies was low and therefore the evidence base for exercise interventions was rated as poor for all interventions and outcomes. Apart from this, the description of training parameters was generally unsatisfactory and there is a lack of uniformity with regard to the use of outcome measures. Suggestions for improving study methodology and training theory were proposed in order to help this field forward.

Besides late training effects that exercise may have, exercise also may have acute effects in haemophilia patients that might be beneficial. In **Chapter 7** we studied the effect of a strenuous physical exercise on the level of clotting factor (F VIII) in patients with mild and moderate haemophilia A. Patients showed consistently increase in FVIII levels after exercise with a median increase of 2.5 times baseline FVIII activity. Even though these results are promising, the practical value of these findings requires further study.

General Discussion

Evaluation of functional health status in haemophilia

Historically, the evaluation of health status has been mainly focused on aspects relating to joint structure and blood coagulation. Consequently, the evaluation of functional ability in haemophilia has long been disregarded. In the past two decades, alongside with the introduction of the ICF model by the World Health Organization, functional ability more and more became the measurement tool for functional ability and consequently were included in studies on haemophilia [1-3]. The (Childhood) Health Assessment Questionnaire ((C)HAQ) is an example of a measure of functional ability that has been "borrowed" to use in haemophilia patients and has served quite well. However researchers increasingly emphasize the need for more haemophilia specific tools, especially on the level of activities [4,5]. In this light, with the development of the Haemophilia Activities List (HAL) [6,7] and consequently the PedHAL [8] we did met this need.

Transition from PedHAL to HAL

With the development of the PedHAL (Chapter 3) changes were made to the content of the HAL, however leaving intact the basic structure as well as many items of the HAL. On the one hand, as intended, these changes to the PedHAL made it more suitable for use in children and adolescents. On the other hand, scores of the PedHAL may not fully be compatible with the HAL. We are aware of this, and this may be object of study in coming decade. With the long-term use of these two measures, combined and maybe simultaneously in certain ages, researchers may be able to pinpoint the specific relationship of PedHAL and HAL scores. The issue of transition from adolescent to adult health status measurement is pursued in other areas as well. For instance the Stanford Health Assessment Questionnaire (HAQ) was modified for children (CHAQ) in 1994 by modifying its content [9]. Researchers nowadays are still in debate how the transition from one the CHAQ to HAQ must be dealt with appropriately [10].

Core-set of outcome measures

It is good news that in the past decade, researchers worldwide have took on the challenge to create and test haemophilia specific outcome measures [6-8,11-17]. Further refinement and testing of the psychometric properties of these tools is in progress. More widespread use of these tools will enable sharing of data across the

world, so promoting best practice and ultimately enhancing patient care [18]. In this light it is encouraging to note that the HAL has already been included in several clinical trials [19,20]. Furthermore, the HAL and PedHAL are currently included in a Canadian study on the efficacy of a new clotting factor product. We anticipate that the data from this trial will give us additional insight into the psychometric properties of these instruments. Ultimately these efforts may lead to a disease specific core-set of outcome measures for children and adults with haemophilia. Currently, there already are good examples on how such a core-set could be developed properly. In the field of (paediatric) rheumatology, for example, the OMERACT and PRINTO initiatives have proven to be successful ways of selecting the best possible outcome measures (in terms of psychometrics and feasibility) based on literature and expert opinions [21,22]. The World Federation of Haemophilia (WFH) could be the leading organization for the development of such a core-set. Currently the WFH facilitates the sharing of newly developed haemophilia specific measurement tools by providing them in an online compendium of outcome measures. In this compendium instruments are provided along with details on psychometric properties, target population and practical details (such as duration of testing). The compendium is publicly available on the WFH web site [23].

Physical activity and haemophilia

In the past and before the introduction of prophylactic treatment, persons with severe haemophilia were discouraged from participating in physical activity because of the risk of bleeds [24]. After the introduction of prophylactic treatment in the late 1950s and onward, attitude towards participation in physical activity has been changed and patients were able to participate in a larger range of physical activities with fewer bleeds.

Benefits of physical activity

Patients with haemophilia should be encouraged to participate in regular physical activity, tailored to their health status and personal lifestyle [3,4]. An active lifestyle is important because it has numerous health benefits, especially for primary and secondary prevention of chronic diseases (e.g., cardiovascular disease, diabetes, cancer, hypertension, obesity, depression and osteoporosis) and premature death [25]. Specific knowledge on the effectiveness of exercise interventions in patients with haemophilia remains unclear due to the lack of high quality studies on this topic as shown and described in Chapter 6 of this thesis. Although the formal

evidence base is poor, exercise interventions or physical therapy are considered important, potentially effective and inexpensive options to treat patients with haemophilia in regions where clotting factor is not readily available [26-29]. The importance of exercise for developing countries, where the supply of factor concentrates is inadequate, is underlined by our findings in patients with mild and moderate haemophilia. In Chapter 7 we presented an increase of factor VIII of 2.5 times baseline values after vigorous physical exercise in adult patients with moderate and mild haemophilia A. Such increased levels of FVIII might lead to a reduced bleeding risk in mild and moderate patients. Moreover, such findings may add to the positive image of physical activity in patients with haemophilia.

Secondary prevention

With reduced morbidity of the musculoskeletal system, as seen in children on prophylaxis, attention may partly shift to health-related fitness and prevention of secondary diseases, such as cardiovascular disease, diabetes, cancer etcetera. Increasingly, research focuses on habitual physical activity levels in haemophilia. Recent studies show that adolescent patients with haemophilia spend more time watching television and playing video-games than healthy peers [30]. On the contrary, the children in the study presented in Chapter 5 were as active as the general population. This is not a common finding in children with chronic disease. Reduced physical activity levels have been reported in many chronic conditions such as Juvenile Idiopathic Arthritis [31], Cerebral Palsy [32] and Spina Bifida [33]. This relatively high level of activity is good news for the patients, as there is evidence that inactivity in children with haemophilia increases the risk of low bone mineral density [34-36]. We should be aware of the fact that the majority of the Dutch children (both healthy and those with haemophilia) do not meet the recommended level of physical activity [37]. Concurrently, the number of obese patients with haemophilia in the Netherlands is rising very rapidly. In adult patients with haemophilia, the prevalence of overweight (BMI 25-30 kg/m^2) increased from 27% to 35% and the prevalence of obesity (BMI $\geq$30 kg/m^2) doubled from 4% to 8%, which is comparable with the general population [38]. The prevalence of obesity in Dutch children with haemophilia even tripled (from 2% to 6%) in 10 years, which is alarming [38]. In the United States it is even worse: In the state of Mississippi, 51% of the patients with haemophilia were either obese or overweight [39]. The prevalence of obesity in the adult (>20 years old) patients with haemophilia was 36% and an additional 32% were overweight. In the children/adolescents (age 2–19.9 years), 21% were obese with a further 16%

overweight. The highest prevalence in this group occurred in the 11–19.9 year age range [39]. Being overweight or obese has a profound effect on functional ability [20,40] and quality of life [40] in patients with haemophilia by aggravating pre-existing arthropathy [41] and predisposing aged patients to cardiovascular disease [42]. Strategies to combat overweight in patients with haemophilia are therefore urgently needed [38]. It might be necessary to expand follow-up procedures with specific counselling on diet and physical activity to be able to counteract this growing number of patients being overweight or obese.

Risks of physical activity

There is emerging data on the bleeding risk of different physical activities. For example, a recent study in children suggested that engaging in vigorous activities did not lead to a greater number of bleeding episodes when compared to non-vigorous activities. However, vigorous activities led to a higher percentage of bleeds related to a trauma [43]. There is some evidence that children with severe haemophilia on prophylaxis participating in high impact sports do not have increased joint bleedings than children that are participating in low impact sports [44]. Clearly, more prospective studies are needed to elucidate the causal relationship between activities and bleeding episodes in children with haemophilia. Hopefully this will provide better insight into the risks that children with haemophilia encounter by engaging in certain physical activities. Objective activity measures such as accelerometers are becoming more and more advanced, and recent studies have shown that it is possible to identify specific activities from accelerometer data quite accurately [45,46].

Accelerometers therefore might be very useful tools to track physical activity behaviour in patients with haemophilia. New media such as Internet portals or text messaging may further help in this regard. Recently a study design was published on the estimation of bleeding risk through self report of activities and bleeds via text messaging by mobile phone by children with haemophilia [47].

In our systematic review on exercise interventions (Chapter 6) complications were reported in two studies: Greene et al. [48] reported that some patients with bad joint status reported peri-patellar pain during exercises, and Gurcay et al. [49] reported 2 patients developing a joint haemorrhage during the intervention, even though they received prophylaxis during the training programme. The majority of the studies reported that the exercise intervention did not have any adverse effects.

With regard to sports, there is still great debate on the risks. Several institutions have presented tables or overviews on the level of risk that certain sports might have, such as the World Federation of Haemophilia (WFH) [50], The Haemophilia Society [51], The National Haemophilia Foundation [52], and Fit for Live [53]. However these institutions are far from reaching a consensus. For example: soccer is rated as "high risk" by Fit for Life, whereas by the WFH and the NHF it is rated as "safe with risk". Accordingly, there is a range of other sports were the risk evaluation is conflicting. Therefore, rather than making recommendations about all sports and apply them to everyone, it may be more useful to match the person and the activity according to the biomechanical requirements of the sport and the physical abilities of the participant [54].

Overall, the impression is that the benefits of physical activity in patients with haemophilia outweigh the risks. Especially when proper precautions are taken and activities are suited to the physical ability of the patient. General textbook recommendations for patients with haemophilia are: wearing proper protective clothing, performing a proper warm-up and in case of severe haemophilia and using prophylaxis before engaging in strenuous physical activities or sports.

Suggestions for future research

This thesis describes the first steps in the development of a disease specific instrument to measure functional ability in children with haemophilia: the PedHAL. Although the studies in this thesis show that the PedHAL is a promising tool, further improvements could be made. Possibly reliability could by improved by removing some items that seem redundant. Reducing redundancy of this instrument by deleting of items/activities however may result in loss of content validity. This issue has to be addressed in future studies. Furthermore the content may have to be adapted in some way to make it cultural appropriate when introduced elsewhere. Possibly, the eventual PedHAL will consist of a "common trunk" with additional culture specific activities. We encourage further refinement of this tool by international collaborators to improve the outcome evaluation of the children with haemophilia around the world. It can be expected that the PedHAL will evolve over time just as for example the CHAQ, which has been modified by extending it with extra (more physically challenging) items as well as by adjusting the scoring system. Maybe by developing a short form or by applying computer adaptive testing procedures, the usability of the PedHAL could be further improved. As stated earlier, a core-set of outcome measures across all levels of the ICF is required to enhance comparability of study results in patients with

haemophilia. When this set is identified specific procedures such as ICF linking [55,56] could be used to determine whether all aspects of functional health, that are relevant for haemophilia, are adequately covered.

Furthermore, we need to improve our understanding of the impact of exercise and physical activity both in patients with and without prophylactic treatment. For those patients without prophylaxis much more evidence is needed on what type of interventions are the most beneficial. The evidence base should be expanded with high quality exercise intervention studies, as is outlined in Chapter 6. In addition, apart from developing a basic core-set for evaluating functional health status in patients with haemophilia, uniformity on the outcome measures with respect to *exercise tests* is also needed, because it will enhance the comparability of outcomes across studies with haemophilia patients. A Delphi procedure with researchers and clinicians could lead to a core-set, which could enhance uniformity in reporting trials on the effects of exercise interventions. Such a Delphi procedure has recently been published within the field of Cerebral Palsy and could serve as good example [57]. For patients on prophylaxis, the focus increasingly may be on aspects of health related physical fitness that have long been out of scope for patients with haemophilia because of the primary need to treat bleeding episodes and joint pathology. A conceptual model such as proposed by Bouchard and Shepard [58] could be very helpful in defining new research questions on the specific relationship of physical activity, health related physical fitness and well being and mortality. Finally, clinical exercise physiologists may become increasingly important in this particular research area because they are equipped with knowledge on (patho-) physiology as well as with general principles of exercise testing and programming. Research in the field of clinical exercise physiology has proved its merits and will continue to show that exercise should be an integral part of medical practice: exercise *is* medicine.

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Samenvatting (Dutch summary)

In **hoofdstuk 1** wordt een introductie gegeven over hemofilie, het meten van de functionele gezondheid en de rol van fysieke activiteit bij patiënten met hemofilie. De doelstellingen van dit proefschrift worden gepresenteerd.

In **hoofdstuk 2** wordt een cross-sectionele studie beschreven over de relatie tussen aspecten van gewrichtsstatus en functionele mogelijkheden. Analyse van data van 226 kinderen die intensief behandeld werden met stollingsfactor, laat zien dat er over het algemeen weinig associatie is tussen gewrichtsstatus en functionele mogelijkheden. Kleine, maar significante associaties werden gevonden tussen aspecten van enkelgewrichtstatus en het uitvoeren van taken waarbij de onderste extremiteiten betrokken zijn. Deze bevinding laat zien dat de enkels mogelijk extra aandacht verdienen bij de klinische follow-up van deze kinderen. Deze studie laat ook zien dat een hemofiliespecifieke uitkomstmaat voor functionele mogelijkheden gewenst is en vooral nuttig zou kunnen zijn bij kinderen met een relatief goede gewrichtsstatus. In **hoofdstuk 3** en **4** wordt de ontwikkeling van de Pediatrische Hemofilie Activiteiten Lijst (PedHAL) beschreven, waarmee aan deze wens tegemoet wordt gekomen.

Hoofdstuk 3 beschrijft de ontwikkeling en het testen van de PedHAL bij Nederlandse kinderen met hemofilie. De structuur en een groot deel van de inhoud is verkregen vanuit de Hemofilie activiteiten lijst (HAL). Voorts zijn er items van andere pediatrische vragenlijsten over fysieke activiteiten toegevoegd. Gezondheidsprofessionals, patiënten en ouders hebben deze versie beoordeeld. Een pilot-test bij 32 Nederlandse kinderen werd uitgevoerd om de scoreverdeling, de constructvaliditeit en de betrouwbaarheid te meten. De analyses laten zien dat het afnemen van de PedHAL haalbaar is en dat de scores in het hoge gedeelte van de schaal lagen, wat overeenkomt met een goede functionele status. De PedHAL correleerde met scores van gewrichtsonderzoek en met de subschaal ‘fysieke functie’ van de kindergezondheidsvragenlijst (CHQ). De PedHAL correleerde niet met de mentale en gedrags-subschaal van de CHQ. Deze bevindingen ondersteunen de validiteit van het construct van de PedHAL als maat voor functionele gezondheidsstatus. De test-hertest overeenkomst was goed. We concluderen dat de PedHAL een veelbelovend instrument is, maar dat meer onderzoek nodig is in populaties met een grotere mate van functionele beperking. Daarom beschrijven we in **hoofdstuk 4** het testen van de psychometrie van de PedHAL in een groep Roemeense kinderen die geen bloedingsprofylaxe krijgen. Kinderen die in het

revalidatiecentrum in Buzias (Roemenië) worden behandeld werden geïncludeerd. De constructvaliditeit van de PedHAL werd bepaald door het gelijktijdig scoren van zowel objectieve als subjectieve maten van fysiek functioneren en functionele mogelijkheden. De reproduceerbaarheid werd getest door een 3-daagse test-hertest. De responsiviteit van een revalidatiebehandeling werd gemeten met de PedHAL en met een instrument voor gewrichtsstatus (Haemophilia Joint Health Score; HJHS). De mediane PedHAL score was bijna 20 punten lager dan bij de Nederlandse patiënten. De PedHAL correleerde met gewrichtsstatus, met functionele onafhankelijkheid en met de subschaal 'fysieke functie' van de CHQ. De PedHAL correleerde niet met de mentale en gedrags-subschaal van de CHQ en met een functionele wandeltest. De test-hertest betrouwbaarheid was goed, terwijl de test-hertest overeenkomst op twee opeenvolgende testen een aanzienlijke variatie vertoonde. Een kort revalidatieprogramma leidde tot een kleine verbetering in de HJHS scores, terwijl de PedHAL scores gelijk bleven. We concludeerden dat de constructvaliditeit en de test-hertest betrouwbaarheid goed waren en dat de test-hertest overeenkomst enige variatie vertoonde. Daarom is de PedHAL momenteel waarschijnlijk beter geschikt voor onderzoeksdoeleinden dan voor het monitoren van individuele patiënten in de klinische praktijk.

In **hoofdstuk 5** hebben we onderzocht aan welke fysieke activiteiten Nederlandse kinderen met hemofilie deelnemen, hoe hun activiteitenniveau zich verhoudt tot de nationale richtlijn en hoe hun cardiorespiratoire fitheid is ten opzichte van referentiewaarden. Verder hebben we geanalyseerd of er een associatie is tussen de intensiteit van de fysieke activiteiten, de gewrichtsstatus en cardiorespiratoire fitheid. Er werd gevonden dat kinderen met hemofilie net zo actief zijn als de normale populatie en dat ze een normale cardiorespiratoire fitheid hebben. Kinderen met ernstige hemofilie zwommen meer en voetbalden (in wedstrijdverband) minder dan de kinderen met een mildere vorm van hemofilie. We vonden geen duidelijke relatie tussen het activiteitenniveau, de gewrichtsstatus en de cardiorespiratoire fitheid, wat mogelijk verklaard kan worden door een relatief goede gewrichtsstatus en de matige betrouwbaarheid van de vragenlijsten om zelf gerapporteerde fysieke activiteit te meten. In aanvulling op de gebruikelijke fysieke activiteit, kan fysieke inspanning ook aangeboden worden op een gestructureerde manier door middel van bewegingsinterventies. Om de effecten van bewegingsinterventies beter te begrijpen bij patiënten met hemofilie hebben we een systematisch literatuuronderzoek uitgevoerd in **hoofdstuk 6**. Uiteindelijk voldeden negen artikelen aan onze inclusiecriteria en werden deze geïncludeerd in een kwalitatieve analyse. Over het algemeen was het evidentieniveau en de

kwaliteit van de geïncludeerde studies laag en daarom werd de evidentie voor alle interventies en uitkomstmaten beoordeeld als “slecht”. Daarnaast werden de trainingsparameters in de geïncludeerde studies niet adequaat beschreven en is er een gebrek aan uniformiteit ten aanzien van de gebruikte uitkomstmaten. Suggesties voor het verbeteren van de studiemethodes werden voorgesteld om dit veld verder te helpen.

Naast late trainingseffecten, kan inspanning ook acute positieve effecten hebben bij patiënten met hemofilie. In **hoofdstuk 7** bestudeerden we het effect van een zware lichamelijke inspanning op het stollingsfactorgehalte (FVIII) in het bloed van patiënten met milde of matige hemofilie A. Patiënten lieten een consistente toename zien van FVIII na inspanning. De mediane toename was 2.5 keer de uitgangswaarde van FVIII activiteit. Hoewel deze resultaten veelbelovend zijn, is er meer onderzoek nodig om de klinische betekenis van deze bevindingen voor patiënten aan te tonen.

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Curriculum Vitae

De auteur van dit proefschrift werd geboren op 17 november 1981 te Hoorn (NH). Hij volgde het middelbaar onderwijs (VWO) op het Martinus College in Grootebroek en behaalde het eindexamen in 2001. Aansluitend begon hij aan de studie Bewegingswetenschappen aan de Vrije Universiteit te Amsterdam. Na het behalen van de propedeuse werd gekozen voor de afstudeerrichting “bewegen in de context van sport”. Het doctoraalexamen werd behaald in 2006. De eerste onderzoekservaring werd opgedaan tijdens enkele korte dienstverbanden bij de faculteit Bewegingswetenschappen. In november 2007 kwam hij in dienst bij het Kinderbewegingscentrum van het Wilhelmina Kinderziekenhuis, onderdeel van het Universitair Medisch Centrum in Utrecht. Daar is hij gestart met zijn promotieonderzoek onder leiding van Prof. dr. P.J.M. Helders, waarvan de resultaten zijn beschreven in dit proefschrift. Daarnaast heeft hij zich, onder leiding van Dr. Tim Takken, bekwaamd in de klinische inspanningsfysiologie. Momenteel is hij in dienst van het Nederlands Kanker Instituut - Antoni Van Leeuwenhoek Ziekenhuis (NKI-AVL) in Amsterdam. Daar werkt hij als coördinator en onderzoeker aan een project voor patiënten met borst- of longkanker. Doel van het project is om door middel van een internetportaal patiënten beter te informeren en ze te ondersteunen om fysiek actief te worden of te blijven.

List of publications

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