

Musculoskeletal Pathologies in Children with Haemophilia Evaluated using a Standardised Physical Joint Scoring System to Assess Disability

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Abstract

Repeated bleeding into the joints leads to the development of chronic and progressive joint disease in 90% of people with severe haemophilia. Owing to recurrent haemarthroses, musculoskeletal outcome remains an important hallmark of treatment efficacy in haemophilia. Physical joint assessment is commonly used to measure structural and functional joint damage. With the development and introduction of prophylaxis, the most widely used instruments for the assessment of haemophilic arthropathy were found to lack sensitivity to detect the earliest signs of joint disease. To address these inadequacies, a new international consensus tool, the Haemophilia Joint Health Score (HJHS), was developed. The HJHS appears to be a sensitive, reliable and valid tool. However, the HJHS needs further evaluation in various patient populations to assess its applicability and usefulness.

Keywords

Haemophilia Joint Health Score (HJHS), haemophilia, joint assessment, musculoskeletal assessment, patients with haemophilia

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Patients with haemophilia experience a spectrum of bleeding manifestations that occur either spontaneously or after minimal trauma. Examples of bleeding range from life-threatening bleeding such as intracranial haemorrhage to less severe bleeds such as easy bruising or mucosal bleeding. Joint haemorrhage or intra-articular bleeding (haemarthrosis) accounts for >90% of all bleeding events in patients with severe haemophilia (as defined by a circulating clotting factor activity of <0.01IU/ml).¹⁻³

Bleeding into joints occurs spontaneously with a frequency that usually ranges from 20–30 to 50 times per year.⁴⁻⁶ This leads to a painful chronic joint disease affecting 90% of people with severe haemophilia.⁷ Close to 80% of recurrent joint bleeds have been found to take place in joints of the extremities, in particular the elbows, knees and ankles,^{1-3,8,9} but may occur into almost any joint.^{10,11}

Early bleeds into joints are often observed when a child starts walking,¹²⁻¹⁴ but the age of the first bleed varies among individuals and has been reported to occur between one and five years, with a higher frequency between 1.2 and two years of age.¹⁵ Over a period of time, recurrent bleeds into the same joint result in progressive joint damage and the development of haemophilic arthropathy, which is characterised by synovial hypertrophy, cartilage damage, loss of joint space and subchondral bone changes.¹⁶

While the pathogenesis of haemophilic arthropathy is increasingly better understood, the exact mechanisms that result in the blood-induced joint damage, in particular the early changes in the joint,

remain to be fully elucidated. It appears that this is a complex and multifactorial process involving both inflammatory synovium-mediated components and degenerative cartilage-mediated changes.¹⁷⁻²³ There is evidence from *in vitro* studies to suggest that immature articular cartilage may be more susceptible to blood-induced damage than mature articular cartilage.²⁴ The risk of joint damage increases proportionally with the number of bleeding episodes. By contrast, initiation of progressing and irreversible joint changes may occur after only a small number of joint bleeds.²⁵

Furthermore, changes demonstrable by magnetic resonance imaging (MRI) may be found in patients who have never reported a joint bleed, suggesting the existence of microhaemorrhages or subclinical haemorrhages into the joints that may cause deterioration of joints with no historical evidence of haemarthrosis.²⁶⁻²⁸

Recurrent bleeding into joints results in progressive and irreversible changes leading to the development of the classic haemophilic arthropathy. Once established, there is no chance of spontaneous resolution and the condition may even progress during the use of preventative treatment.²⁹

Musculoskeletal Outcome Assessment

Recurrent haemarthroses mean that musculoskeletal outcome remains an important hallmark of treatment efficacy in haemophilia. Musculoskeletal damage is a progressive and irreversible disease that usually occurs after a limited number of joint haemorrhages in childhood, usually as early as the second decade of life.³⁰

Table 1: Studies that Have Used the Haemophilia Joint Health Score for Assessing Musculoskeletal Status in Patients with Haemophilia

Authors, Year	Number of Patients	Type of Haemophilia	Treatment Regimen	Mean Age (Range)	Median/Mean HJHS
Hilliard et al., 2006 ⁸	8	Severe	Prophylaxis	8.7 (4–12)	15 (First day) 14 (Second day)
Chen et al., 2008 ⁵²	20	Severe/moderate/ unknown: 5/13/2	On-demand/sporadic/ none	NS (5–17)	12
Engelbert et al., 2008 ⁵⁰	47	Severe/moderate/mild: 21/7/19	Prophylaxis/on-demand: 21/26	NS	NS (0–6)
Trakymiene et al., 2010 ⁵³	20	Severe	On-demand	11.5 (4–17.2)	24.5 11.6 (<10 years of age) 31.5 (≥10 years of age)
Christoforidis et al., 2011 ⁵¹	26	Severe/moderate	Prophylaxis	12.08 (NS)	8.27 (severe) 4.83 (moderate)
Bladen et al., 2010 ⁵⁴	39	Severe	Primary prophylaxis	10 (4–18)	1 (4–6 years of age) 4 (14–18 years of age)
Feldman et al., 2010 ⁴⁹	226	Severe/moderate/mild	Prophylaxis/on-demand	10.8	5 (in severe with primary prophylaxis) 9 (in severe with secondary prophylaxis) 11.5 (in severe with on-demand therapy)

HJHS = Haemophilia Joint Health Score; NS = not specified.

Until recently, most long-term musculoskeletal outcome studies in haemophilia have used clinical and radiological scores to determine the efficacy of different treatment regimens. Physical joint assessment, being readily available and inexpensive, is commonly used to measure structural and functional joint damage. The physical status of the musculoskeletal system can be judged by quantifying the extent of musculoskeletal damage.

Several systems have been adopted in the past as instruments for musculoskeletal assessment in children and adults. The earliest reported and most widely used instrument for the assessment of haemophilic arthropathy is the World Federation of Hemophilia (WFH) Physical Examination (PE) scale, which was developed in the early 1980s for use in persons with haemophilia worldwide, primarily in the evaluation of adults.³¹ This instrument was developed in the pre-prophylaxis era, at a time when much lower quantities of replacement therapy were available for the management of haemophilia patients. Severe joint disease was to be expected in haemophilia patients at that time. The global application of this tool^{29,32–34} has allowed the natural history of haemophilia to be documented and has determined the progressive improvement in outcomes that has been achieved with comprehensive haemophilia care.^{17,32} However, with the introduction of prophylaxis and heightened interest in preserving joints and preventing complications related to recurrent haemarthroses, the WFH PE scale was found to lack sensitivity in detecting the earliest signs of joint disease and to be inadequate for the evaluation of joints in children.^{17,35,36} The WFH instrument contains many tasks that cannot be performed by young children owing to their developmental immaturity, and was not designed to detect changes that are part of normal physiological musculoskeletal development in healthy young children.^{37–39} Furthermore, the score does not assess muscle strength – an important function that affects physical activity.

To address these inadequacies, the system was repeatedly modified from 1993 onwards by adding analysis of gait and strength, among

other factors, in US and Canadian haemophilia centres.^{35,40,41} Additionally, in the late 1990s Swedish researchers implemented similar revisions to increase the sensitivity of the WFH PE tool.⁴² Eventually, the WFH scale with its various modifications was judged inadequate for evaluating the results of prophylaxis. In addition, the WFH PE tool lacks documented reliability and validity.⁴³ Subsequently, progress has been accomplished through work delivered by multinational expert groups reviewing the existing joint health scoring systems to produce consensus on the most relevant items to be adopted internationally.^{8,40} The Physiotherapy Expert Working Group of the International Prophylaxis Study Group (IPSG) was formed by a group of interested expert clinicians and scientists,⁴⁴ who combined and harmonised existing joint health scores (WFH, Colorado and Stockholm) to develop a more sensitive tool. In 2003, a new international consensus tool, the Haemophilia Joint Health Score (HJHS) version 1.0, was announced. The aim was to produce a score that would be sensitive to early change, accounting for normal development in children and reliable, valid and practical to administer. It aimed to provide an international scoring instrument for children with haemophilia as a measure of joint health in order to evaluate and monitor the effectiveness of haemophilia treatment.^{8,35,36,44–46}

Reliability and Validity of the Haemophilia Joint Health Score

The HJHS is an 11-item scoring tool for assessing joint impairment in children four to 18 years of age.⁸ The tool focuses on the six joints most affected by haemophilia: ankles, knees and elbows. Each of the six index joints is assessed individually on different items and numerically scored in categories of severity. A global gait score (walking, stairs, running and hopping on one leg) is assessed separately. The total joint score (the sum of the six joint scores) and the global gait score, when combined, provide an overall total score ranging from zero to 124 in version 2.0 (148 in version 1.0), where a score of zero corresponds to no identifiable joint impairment. The new scale was piloted during a meeting in September 2003. Four physiotherapists from Canada, the US and Sweden conducted an initial reliability study of the HJHS

in eight paediatric patients. The findings of the reliability study of the HJHS version 1.0 indicated that the reliability of this tool was excellent, with a very high interobserver reliability co-efficient of 0.83 and a test-re-test co-efficient of 0.89.^{8,45} In 2005, a manual and a supporting HJHS instructional video were produced in order for non-IPSG evaluators to reliably make use of the HJHS. Another reliability study on the HJHS was performed in November 2009 in China.⁴⁷ Four physiotherapists from four Chinese haemophilia treatment centres examined eight boys six to 17 years of age with haemophilia A on two consecutive days using the HJHS version 2.1. The study subjects presented with variable degrees of joint damage. The overall reliability was excellent and similar to the findings of the initial reliability study of the HJHS, with an interobserver co-efficient of 0.90 and a test-re-test co-efficient of 0.91.

In 2006–2007, a two-year multicentre validation study of the HJHS was carried out.^{48,49} This study was undertaken to establish whether the HJHS could accurately measure joint status in patients with mild, moderate and severe haemophilia A or B. The validity and sensitivity of the original WFH scale were compared in parallel. Two hundred and twenty-six patients (mean age 10.8 years) from five centres (Stockholm, Utrecht, Denver, Montreal and Toronto) with mild (17%), moderate (15%) and severe (68%) haemophilia were included in this study. The six-joint HJHS was found to correlate highly with the WFH scale; however, the HJHS was 97% more accurate than the WFH scale in distinguishing among mild, moderate and severe disease, even if the majority of the severe patients were receiving prophylaxis therapy ($T=5.80$; $p=0.06$). The median (interquartile range [IQR]) HJHS for severe haemophilia subjects was six (11), for moderate four (eight) and for mild three (eight). The HJHS was also 74% more efficient than the WFH scale at differentiating individuals treated with prophylaxis from those who rarely bled and were never treated with prophylaxis ($T=7.32$; $p=0.007$). The median (IQR) HJHS for subjects treated with prophylaxis was six (11), and for those never treated with prophylaxis three (eight). When considering only those subjects with severe haemophilia, the HJHS was 63% more efficient than the WFH scale at differentiating patients treated with primary prophylaxis (median HJHS 5.0) from those treated with secondary prophylaxis (median HJHS 9.0) as well as from those treated on demand (median HSHS 11.5) ($T=19.5$; $p=0.00006$). Based on the results of the validation study of the HJHS,⁴⁸ in 2008 the HJHS version 2.0 was developed by removing or modifying redundant or less sensitive items. Other changes included an alteration in the score for joint pain, while the scores for axial alignment, joint instability and gait were removed.

Utility of the Haemophilia Joint Health Score in Different Haemophilia Populations

Measurement of musculoskeletal conditions by applying standardised physical joint assessment tools such as the HJHS is critically important in the continuous surveillance of individuals with haemophilia, especially in children. Data are important for describing the signs of chronic changes related to recurrent joint haemorrhage over time to evaluate and compare the efficacy of various treatment principles.^{19,29}

Since the HJHS is quite a new international instrument for the assessment of joints in children with haemophilia, and was specifically designed to be more sensitive to mild disease in intensively treated boys, the published data quantifying musculoskeletal damage in haemophilia patients using the HJHS instrument come from several studies with patient cohorts who were typically treated with

prophylaxis (see *Table 1*). The HJHS reliability study reported on eight boys on prophylaxis treatment with mild to moderate or severe clinical signs of joint damage and a mean HJHS of 15, ranging from 3.5 to 35 on days one and 14 and from 2 to 27.5 on day two (out of maximum of 148 in the HJHS version 1.0).⁸

The health status of the joints of children with haemophilia was also assessed using the HJHS version 1.0 in a study by Engelbert et al.⁵⁰ Raw scores of the HJHS in 47 Dutch children with haemophilia (21 boys with severe haemophilia receiving factor replacement prophylaxis, seven boys with moderate haemophilia and 19 with mild haemophilia receiving on-demand treatment) showed that these patients had no or minimal joint impairment (raw scores between zero and six).

Joint evaluation using the HJHS was also performed in a comparative study by Christoforidis et al.⁵¹ This study involved 26 patients with haemophilia A and a mean decimal age of 12.08 years (standard deviation [SD] 4.44). Seventeen patients had severe haemophilia A (residual factor activity <1%) and nine had moderate haemophilia A. The mean HJHS for moderate haemophilia was 4.83 (SD 5.27, range 0–15), and for severe haemophilia was 8.27 (SD 6.11, range 0–23; $p=0.24$).

The utility of the HJHS in assessing the health status of the joints was also tested on 20 Chinese children with haemophilia (age five to 17 years, haemophilia A/B: 18/2; severe/moderate/unknown: 5/13/2).⁵² The HJHS score ranged from one to 35 (mean 13.1, median 12, SD 9.03). The investigators stated that the score was significantly higher in older than in younger children, but it was not specified exactly from which age the score was noticed to be higher. The utility of the HJHS was also tested in patients with haemophilia that do not receive preventative treatment. The first report using the HJHS in assessing health status of the joints in patients with the treatment on-demand, sporadic or none of the treatment, comes from 20 Chinese haemophilia children (age 5–17; haemophilia A/B: 18/2; severe/moderate/unknown: 5/13/2).⁵² The HJHS score ranged from one to 35 (mean 13.1, median 12, SD 9.03). Investigators of the latter report stated that the score was significantly higher in older than in younger children, but it was not specified exactly from which age the score was noticed to be higher.

The first study, characterising musculoskeletal damage in severe haemophilia using the HJHS tool in boys treated exclusively by on-demand treatment practices, indicated new scores.⁵³ The mean total HJHS in the study cohort ($n=20$) was 24.5, with a range from five to 50. There was a higher total as well as a higher six-joint HJHS in patients with severe haemophilia and treatment on demand compared with all above-mentioned studies in which the HJHS instrument was used. Overall, 50% of the patients in this study had an HJHS of 25 or higher. Furthermore, the study investigated the progression of haemophilic arthropathy during childhood and puberty, with a particular focus on the age at which remarkable changes occurred, based on the HJHS. The data indicated that a worsening of the HJHS score was noticed with increasing age and that >50% (eight of 13) of the patients ≥ 10 years of age presented with values higher than 30 ($p=0.0002$). The comparison of the mean total HJHS between the two age groups resulted in the detection of significant differences between patients under 10 years of age and older patients, showing that the most risky period and most aggravating development of haemophilic joint damage starts from 10 years of age.

The above results were supported by researchers from the UK.⁵⁴ In 39 boys with severe haemophilia (mean age 10 years, range four to 18) who were receiving primary prophylaxis at 25–40IU/kg at least twice weekly for haemophilia B and three times weekly for haemophilia A, the HJHS ranged between zero and 22, with a tendency to increase progressively with age. Mean values ranged from one in boys four to six years of age to four in boys 14–18 years of age (p=0.08). The HJHS was less than eight in all boys eight years of age and under.

Discussion

The HJHS provides a new clinical measure of joint structure and function in children four to 18 years of age.⁵⁵ It was created to provide a reliable international measure for quantifying joint damage in children with haemophilia. As seen from the above-mentioned studies, the results of the HJHS have been proved to be highly reliable.^{8,47} Furthermore, the HJHS was also validated by the International Haemophilia Prophylaxis Study Group.⁴⁹ The findings reported in these studies should be considered in the light of possible limitations since the physiotherapists participating in the studies were highly experienced and personally involved in the development of the HJHS. On the other hand, the HJHS has now been taught in workshops worldwide and appears to be easily adopted, even by physiotherapists with limited experience in haemophilia.⁴⁹

The results of the studies published to date indicate that the new joint assessment tool enables the detection of subtle and early signs of joint damage in intensively treated boys, and also illustrates the differences among patients with mild, moderate and severe haemophilia based on HJHS. This was demonstrated mainly in the studied subjects with severe haemophilia on prophylactic treatment in countries where factor concentrates were widely available. It is a reasonable group to study since the HJHS was designed specifically to be sensitive for mild joint changes in patients receiving prophylaxis. However, the application of the HJHS tool in a study of patients with severe haemophilia who were exclusively receiving treatment on demand demonstrated that the HJHS is also a useful and effective tool in evaluating musculoskeletal outcome following an on-demand-based treatment approach in patients with existing joint damage. This

shows that the new instrument might be equally appropriate for screening children on prophylactic treatment as well as those using on-demand regimens. The findings from these studies showed that scores were higher in patients using treatment on demand compared with prophylaxis. However, in order to understand the influence of different treatment regimens or management as determined by the HJHS, studies with higher numbers of patients are required. It remains to be seen how the HJHS should be interpreted in different treatment populations with haemophilia.

Findings based on the HJHS also suggested that the HJHS tool may be sensitive to the progression of joint disease with age in haemophilia. An HJHS utility study in episodically treated boys with severe haemophilia⁵³ confirmed that joint damage develops slowly, over decades. The HJHS increased as a sign of progressing haemophilic arthropathy, which seemed to occur from the age of 10 onwards.

Joint abnormalities were minimal on examination using the HJHS in very young children – even those receiving on-demand treatment. This observation could lead to the erroneous assumption that episodic therapy in young children with haemophilia is somehow effective. Furthermore, the HJHS was found to increase progressively with age even in boys with severe haemophilia who were receiving prophylaxis.⁵⁴ This observation supports the usefulness of the HJHS in clinical practice to monitor joint status in children receiving prophylaxis.

Conclusions

In this era of prophylaxis, a joint evaluation system that is capable of detecting early and subtle changes in joint health and function is of paramount importance. The HJHS is a sensitive, reliable and valid tool; however, it needs further evaluation in different patient populations and in centres that were not involved in its design to assess its applicability and usefulness in clinical practice and research. Furthermore, a case–control comparative study of clinical outcomes using the HJHS in paediatric severe haemophilia patients treated with prophylaxis compared with those managed by on-demand treatment would be valuable to extend our understanding of the HJHS in normal and damaged joints. ■

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