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REVIEW ARTICLE

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# Clinical relevance of 3D gait analysis in patients with haemophilia

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Haemophilia is characterized by a congenital deficiency of clotting factor VIII or IX. One of the consequences of haemophilia is joint bleedings. Repetitive haemathroses induce cartilage damage and chronic synovitis leading to joint deterioration, and to definitive haemophilic arthropathy which is source of walking disability. Three-dimension gait analysis (3DGA) appears particularly relevant in the case of haemophilia because it allows an evaluation of several joints in weight-bearing situations. The purpose of this study was to review the interest and the contribution of 3DGA in the management of patients with haemophilia. The greatest interest of gait analysis would be to detect early walking changes with a non-invasive and well-tolerated examination, especially in paediatric population. In adulthood, this technic may be also useful to help detect walking worsening in patients known to have already arthropathy. However, it takes time to realize and needs expensive equipment, which limits its possibility of routine use. Although generalizations of these results remain difficult, especially to compare patients with haemophilia to normal population. Indeed, in the studies, patient groups are small and usually heterogeneous in terms of age and target joints. It certainly results of the rarity of the disease. So, it could be interesting to perform a study with a larger cohort in order to allow subgroup analysis, helping to define clearly the place of 3DGA in the strategy of haemophilia evaluation.

**KEYWORDS**
adults, arthropathy, children, gait analysis, Haemophilia

## 1 | INTRODUCTION

Haemophilia is characterized by a congenital deficiency of clotting factor VIII (haemophilia A) or IX (haemophilia B). Disease expression depends on the level of clotting factor in the blood (severe <1%; moderate 1%-5%; mild >5%).[1] One of the consequences of haemophilia is joint bleedings.[2] The ankle joint and the knee joint are the most common joint affected.[3] First bleedings appear early in life, around 2 years old, during walking acquisition.[4] In the most severe forms, repetitive haemathroses induce early muscle weakness and atrophy,[5] cartilage damage and chronic synovitis that ultimately leads to total joint destruction [6] associated with severe walking disability.[7] Joint health is usually evaluated by clinical examination, clinical score and imaging. However, X-rays only allow the detection of the more advanced signs of joint deterioration and are unable to provide information about early changes. MRI has shown its interest to detect early signs in joint alteration but remains difficult to use in routine practice because of its cost and limited accessibility. Recently, instrumental gait analysis (GA), a more functional approach, has been developed in complex musculoskeletal disorders, especially in case of arthropathy, such as osteoarthritis.[8,9] It has also been proposed in the paediatric population.[10,11] GA appears particularly relevant in the case of haemophilia because it allows an evaluation of several joints in weight-bearing situations. Few studies have been published in patients with haemophilia (PWH), either in the child population or the adult one. The interest of GA is to provide precise information

  

on spatiotemporal, kinematic and kinetic gait characteristics even in case of early damage that could lead to new therapeutic approaches.

The purpose of this study was to review the interest and the contribution of three-dimensional gait analysis (3DGA) in the management of patients with haemophilia and then to assess its clinical relevance. This narrative review was performed with medical databases: PubMed, ScienceDirect and Google Scholar. Article research extended from 2000 to 2017. Multiple searches were carried out using the following parameters: gait analysis, haemophilia or hemophilia, haemophilic arthropathy, kinetic, kinematic and spatiotemporal. This narrative review concerned only original studies. Case reports and small series of cases were not considered in the article selection, and only studies in English language were selected. We chose to distinguish studies dealing with adults and children because it has been previously demonstrated that walking patterns is not completely developed in children before adolescence[12] and that walking parameters are age related in the paediatric population[13] and therefore not comparable to adult walking. We tried to include articles studying separately either children and adolescents (<18 years old) or adults. After identification of key articles, their reference and citation lists were perused for further information sources.

## 2 | GENERAL PRINCIPLES OF 3D GAIT ANALYSIS

Visual gait examination is the first stage of walking evaluation. However, its contribution remains limited due to several reasons such as walking speed and multiple joint impairment. So, GA is used to evaluate walking objectively. 3DGA uses capture motion systems (usually infrared cameras) and is usually associated with force plates or pressure mats which enables clinicians to evaluate simultaneously walking spatiotemporal, kinematic and kinetic parameters, especially in case of complex gait disturbance. Methods could vary according to the use of a treadmill with force transducers or a walkway with force platforms. Some authors couple data from 3DGA to oxygen consumption while walking, in order to evaluate muscle efficiency.[14] Examinations are performed after setting up reflective markers on the skin which allow to model lower limb segments and their 3D moving. With a capture motion system, it is possible to measure joint range of motion and angles during walking. Kinematic parameters give information about joint angles during walking, analysing limb segment movements. The kinetic parameters study the force of interaction between lower limbs and the ground. Data from ground reaction platforms allow to calculate the moments of force at joints using inverse dynamic method. In clinical practice, kinematic and kinetic parameters help to better understand walking disturbance, especially the involvement of the different joints. Indeed, it enables clinicians to distinguish primitive abnormalities (eg, of one or several joints) from the secondary or the compensatory abnormalities that are only the consequence of the first ones—and should not be the target of the treatment. So, with 3DGA, clinicians are able to focus on a particular joint. Moreover, kinematic and kinetic parameters may help to follow objectively the evolution of the walking according to time or after a therapeutic intervention (eg, rehabilitation, drug intake or surgery).

Characteristics and methods of the included studies are provided in Table 1.

## 3 | ARE SPATIOTEMPORAL PARAMETERS MODIFIED IN PWH?

Spatiotemporal parameters are provided by pressure mats and are also calculated with data from 3DGA (kinetic and kinematic data). As these parameters are obtained from 2 different methods, if they are consistent it allows to validate the accuracy of the results from the gait analysis. Spatiotemporal parameters give information about time and length parameters of walking patterns, such as speed, length of the step and timing of gait cycle phases.

### 3.1 | Children and adolescents

Using our parameters of searches, we have identified 6 studies that have been conducted to determine the spatiotemporal parameters of walking in young PWH.[5,15-19] Bladen et al found that boys with haemophilia had significant modifications of temporal walking parameters even if they were clinically asymptomatic.[15] In this study, boys with haemophilia were compared to age and leg length-matched controls. The main results showed a decrease in the stance phase and an increase in the swing phase duration.[15,16] In case of clinically detectable arthropathy (association of clinical and X-ray abnormalities), step length and velocity were significantly decreased and a significant increase was noticed in the swing time, stance time, step time, stride time, base of support, double and single support durations.[15] Recently, Forneris et al[19] confirmed that patients with moderate or severe haemophilia had a decrease in step speed and length and an increase in double support and swing phase duration. They provided sub-group analysis showing that these results were most marked in patients with severe haemophilia receiving immune tolerance therapy and a current inhibitor. Yet, these results were not confirmed by other studies in which no spatiotemporal differences were found between haemophilic boys and controls[5,17,18] (Table 2).

One explanation could be the difference of the boys' mean age. In the studies of Bladen et al[15] and Suckling et al,[16] children were older (from 12.7 years old ± 2.5 to 14.2 ± 2.1) than in the others studies (from 9.1 ± 1.9 to 10.7 ± 1.8). Older children may have experienced more bleeding episodes in their life and had more severe target joints. Furthermore, body dimensions are known to influence spatiotemporal values, especially smaller leg length induce smaller steps and higher frequency of steps.[20] Hof et al[21] provided a calculation to account for inter-individual stature differences, as used by Stephensen et al[17] for all the studied parameters. Bladen et al provided only normalized data for velocity,[15] which is a limit to their conclusions. Forneris et al[19] analysed separately the left and the right sides but did not provide any clear information about

**TABLE 1** Studies characteristics

| Study | Number (n) and type (haemophilia A/B) | Studied Population | Severity: severe/ moderate/mild, (Inhibitor) | Age (years), ± SD or (range) | Methodology | Design |
|---|---|---|---|---|---|---|
| Bladen et al (2007)[15] | 26 (23/3) - 20 with no evidence of Joint pathology and 6 with arthropathy On X-rays | Children | 26/0/0 (6) | Asymptomatic group: 12.7 ± 2.5 (7.5-17.2) Arthropathy group: 14.0 ± 1.6 (12.6-15.3) | Electronic carpeted walkway, walk at preferred speed | Retrospective, age-matched control group. Analysis of the spatiotemporal parameters |
| Stephensen et al (2009)[17] | 14 (NC/NC) | Children | 14/0/0 | 10.70 ± 1.83 | 3DGA, walk at preferred speed on a 7.5 m walkway with 2 platforms of force | Comparison of the leg with a target ankle joint to the same leg of an age-matched control group |
| Stephensen et al (2014)[5] | 19 (NC/NC) | Children | 19/0/0 | 10.37 ± 2.11 | 3DGA, walk at preferred speed on a 7.5 m walkway with 2 platforms of force | Comparison of the leg with a target ankle joint to the same leg of an age-matched control group, research of an association between lateral gastrocnemius US imaging and strength of ankle plantar flexor muscle |
| Stephensen et al (2016)[18] | 21 (16/1?) | Children | 21/0/0 | 9.16 ± 1.94 (6-12) | 3DGA, walk at preferred speed on a 7.5 m walkway with 2 platforms of force | Evaluation of the relationship between gait patterns and muscle strength or function |
| Forneris et al (2016)[19] | 42 (36/6) | Children | 27/6/9 (4) | 10.7 (4-18) | 3DGA, walk at preferred speed with 2 platforms of force | Comparison of the right and left sides to normal values provided by manufacturer |
| Suckling et al (2017)[16] | 14 (NC/NC) | Adolescents | 11/1/2 | 14.29 ± 2.16 (11-18) | 3DGA, walk at preferred speed | Comparison of the leg with the greatest number of joint bleeds to the right leg of an age-matched control group |
| Brunel et al (2017)[34] | 37 (31/6) | Children, adolescents and young adults | 33/4/0 (11) | 13.6 ± 4.4 (6.0-20.3) | 3DGA, walk at preferred speed, 10 m walkway with 1 force plate | Evaluation of the correlation IPSG MRI scoring system to |
| Lobet et al (2010)[25] | 18 (17/1) - with at least one ankle arthropathy | Adult | 16/2/0 (2) | 40 ± 10 (21-60) | 3DGA, walk at preferred speed on a treadmill | Reproducibility evaluation, 2 tests with 18 weeks inter-session |
| Lobet et al (2011)[29] | 21 (20/1) - with at least bilateral ankle arthropathy | Adult | 20/1/0 | 39 ± 9 (21-60) | 3DGA, walk at preferred speed on a treadmill | Prospective, research of an association between structural and clinical alterations, and 3DGA parameters |
| Lobet et al (2012)[26] | 10 (NC/NC) | Adult | NC/NC/NC | 33.0 ± 6.0 | 3DGA, walk at preferred speed on a treadmill | Comparison with a healthy control group, Evaluation of the impact of ankle arthropathy on gait and energetic consumption |
| Lobet et al (2013)[27] | 31 (28/3) | Adult | 27/4/0 | 40 ± 9 (22-61) | 3DGA, walk at preferred speed on a treadmill | Evaluation of patient with multiple haemophilic arthropathies. Study of the impact of multiple arthropathies on 3DGA parameters and the efficiency of walking |

3DGA, Three-dimension gait analysis; NC, not communicated; IPSG, International Prophylaxis Study Group; MRI, Magnetic Resonance Imaging.

the side of the target joints and their location. Sub-group analyses were not performed according to the age, whereas spatiotemporal parameters highly depend on it.[22] The disparity in terms of age is also a limit. Indeed, Forneris et al included patients from 4 to 18 years old while it is well acknowledged that before 7 years old, temporal parameters are highly variable and gait patterns are not matured.[23,24]

So, the results of these studies should be interpreted with caution. Power is often lacking because of the small size of the studied groups and the inhomogeneity concerning the type and number of target joints, sometimes isolated or bilateral ankle bleedings[17] but also sometimes associated with other joints, especially the knees.[15,18]

### 3.2 | Adults

In adult patients, Lobet et al[25] found that 3DGA was a reproducible method. They also found an increase in the stance phase duration after an interval of 18 weeks between two evaluation sessions in PWH, which was in favour of a worsening of the joint damage even on a relatively short time.[25] Yet, the study provided no comparison to a control group or to normal values. General interpretation may be limited by the inhomogeneity concerning the number and the type of arthropathies, all the patients had ankle damage, 16 with bilateral and 2 with unilateral one, but some patients had uni- or bilateral knee or hip arthropathy and others had uni- or bilateral knee or hip replacement. In another study, Lobet et al[26] studied PWH with isolated uni- or bilateral ankle arthropathy compared with healthy subjects. They found that patients with ankle arthropathies had an increase in the stance phase duration. But the conclusions from their results are limited by the very small size of the groups (n = 10 for the PWH group) and it is difficult to be sure that, differences are not partly due to individual variability of walking.

## 4 | IMPACT OF HAEMOPHILIA ON KINEMATIC AND KINETIC PARAMETERS

### 4.1 | Children and adolescents

Literature review showed that some kinematic parameters were modified in PWH (Table 2). Interestingly, patients with an isolated ankle target joints exhibit a significant increase in the knee joint angle during walking.[5,17] Only one study found an increase in the ankle dorsi flexion angle.[5] The knee flexion moment was significantly different in patients with haemophilia. The peak knee flexion moment increased in the initial double support phase, the single support phase and the terminal double support, but ankle joint moments were not modified.[5,17] Suckling et al[16] studied adolescents with haemophilia and used principal component (PC) analysis, which enable them to explore entire kinetic and kinematic waveforms. They found no modification of the kinematic parameters and a decrease in the ankle joint moment PC from the end of the stance phase and the beginning of the swing one, compared to age-matched controls.

These results showed that a full joint evaluation of the lower limbs is necessary and not only of the target joints, because gait modifications are found on the overlying joints. Because of kinetic variability according to age,[13] age-matched controls in case of child studies remain necessary.[5,16,17] However, these studies have several limitations. Stephensen et al[5,17] report studies at the side with the ankle which was considered as the most severely affected, but this does not exclude that the other side was also a target joint and may have influenced overall walking. The results of Suckling et al[16] remain difficult to interpret because the authors did not evaluate inter subject variability and were unable to define if their findings were clinically relevant.

### 4.2 | Adults

Kinematic and kinetic parameters seem to be modified in adult PWH. Lobet et al[26] found that in case of isolated bilateral or unilateral ankle arthropathy, ankle joint angle during the push-off phase decreased and knee joint angle increased during the swing phase. Hip sagittal range of motion decreased during gait. Kinetics variables showed an increase in the ankle peak plantar flexion moment and a decrease in the ankle peak power during the push-off phase. During the swing phase, knee peak power decreased. At the early stage of the swing phase, the hip peak flexion moment and the hip peak power of flexors decreased. In another study,[27] the authors found that in case of multiple joint arthropathies ankle and hip angles significantly decreased during walking but no modifications were found at the knee level.

Differences between these 2 studies may appear surprising especially concerning kinematic parameters at knee level, with no disturbance found in case of multiple arthropathies, whereas some were found in case of isolated ankle arthropathy. Several explanations can be proposed. Firstly, because of the particularly inhomogeneous population,[27] it cannot be excluded that part of the gait results may vary according to the type of joints involved and the severity of the arthropathy in terms of range of motion or pain. Secondly, results are limited because some patients had undergone total knee or hip replacement that could have specifically modified the range of motion of the replaced joint and maybe the gait in general.

## 5 | IS 3DGA CORRELATED WITH IMAGING?

### 5.1 | X-rays imaging

X-rays imaging evaluation remains one of the principal elements of the follow-up of joint status in PWH.[28] However, X-rays imaging provides only structure information of the joint and no information about its function. Lobet et al[29] evaluated the correlation between the ankle function studied by 3DGA and radiological scores, in case of bilateral ankle haemophilic arthropathy in adult PWH. Ankle function

**TABLE 2** Main significant differences observed in spatiotemporal, kinematic and kinetic parameters

| Study | Patients | Subjects' age (years), ±SD | Methods of comparison | Spatiotemporal parameters | Kinematic parameters | Kinetic parameters |
|---|---|---|---|---|---|---|
| Bladen et al (2007)[15] | 26 | *Asymptomatic group (n = 20):* 12.7 ± 2.50<br>*Group with arthropathy (n = 6):* 14.0 ± 1.60 | Age-matched control group | *Asymptomatic group:*<br>**Stance phase decrease**<br>**Swing phase increase**<br>*Group with arthropathy:*<br>**Step length decrease**<br>Velocity decrease<br>Increase of: **Swing phase**, **Stance phase**, Step time increase, Stride time increase, Base of support, Double and Single support | Not applicable | Not applicable |
| Stephensen et al (2009)[17] | 14 | 10.70 ± 1.83 | Age-matched control group | No difference | **Knee joint angle increase** | Peak knee flexion moment increase |
| Stephensen et al (2014)[5] | 19 | 10.37 ± 2.11 | Age-matched control group. | No difference | **Knee joint angle increase**<br>Ankle dorsiflexion angle increase | Peak knee flexion moment increase |
| Forneris et al (2016)[19] | 42 | 10.70 | Normative tables | **Step length decrease**<br>**Swing phase increase**<br>Double support increase | No result statistically significant provided | Not applicable |
| Suckling et al (2017)[16] | 14 | 14.29 ± 2.16 | Age-matched control group | **Stance phase decrease**<br>**Swing phase increase** | No difference | Ankle joint moment decrease |
| Lobet et al (2010)[25] | 18 | 40 ± 10.0 | Paired comparison of the studied group between 2 periods (18 weeks interval) | **Stance phase increase** | **Knee joint angle increase** during swing phase | Not applicable |
| Lobet et al (2012)[26] | 10 | 33.0 ± 6.0 | Control group | **Stance phase increase** | Ankle joint angle decrease during the push-off phase<br>**Knee joint angle increase** during the swing phase | Ankle peak plantar flexion moment increase at the push-off phase<br>Ankle peak power decrease at push-off phase<br>Knee peak power decrease at swing phase<br>Hip peak flexion moment and Hip peak power of flexors decrease at the early swing phase |
| Lobet et al (2013)[27] | 31 | 40 ± 9.0 | Dataset of normal values | No data provided | Ankle and hip angles decrease | No data provided |

Recurrent gait parameters that are usually modified in patients with haemophilia appear in bold characters.

was determined by 3 variables: the ankle active range of motion, the peak plantar flexion moment and the peak power at the push-off phase. The authors found no association between these 3DGA parameters and radiological scores (Arnold-Hilgartner[30] and Petterson scores[31]). These results are consistent with previous conclusions by Rodríguez-Merchán et al,[32] who reported globally preserved joint function with radiological severe damage. It is also consistent with other studies on other arthropathies such as osteoarthritis.[33]

### 5.2 | Ultrasound imaging

Stephensen et al[5] evaluated the correlation between gait and ultrasound lateral gastrocnemius muscle architecture in haemophilic children. Fascicle length was inversely correlated with peak knee flexion moment during initial double support ($r = -.51$; $P < .05$). Fascicle pennation angle was inversely associated with peak ankle dorsi flexion angle ($r = -.71$; $P < .001$); fascicle length was also inversely associated with peak knee flexion moment during single support ($r = -.58$; $P < .01$). A positive correlation was found between muscle thickness and peak knee extension moment during single support ($r = .59$; $P < .01$).

Yet, these results did not allow to know if the modifications in muscle architecture were a consequence of gait disturbance due to joint bleedings or a consequence of previous muscle bleedings or inversely a mechanism to protect joints from new bleedings by reducing constraints on the joints. However, it indicates that alteration of walking patterns is not only the consequences of joint damage but it may also have muscular origins.

### 5.3 | Magnetic resonance imaging

Recently, Brunel et al[34] evaluated the correlation of the IPSG MRI score (International Prophylaxis Study Group Magnetic Resonance Imaging score) of tibiotalar and subtalar joints to 3D rearfoot kinematic parameters in 37 patients (children, adolescents and young adults). IPSG MRI score has been developed to study soft tissues and osteochondral alterations.[35] Rearfoot sagittal range of motion was not correlated with subtalar MRI score and poorly with tibiotalar joint scores ($r$ from −.25 to −.35). Coronal range of motion during the terminal stance phase was positively but poorly correlated with tibiotalar joint MRI osteochondral lesions ($r = .27$, $P = .024$). Subtalar lesions on MRI were also inversely correlated to Coronal range of motion during loading response phase ($r = -.28$, $P = .018$).

So, these results seem to be in favour of a poor correlation between MRI findings and some kinematic variables. However, conclusions are limited. Indeed, the number of pathological joints was very low; of the 73 ankles studied, only 14 had both MRI and clinical signs, and 41 were considered normal. Furthermore, although some kinematic parameters are correlated to MRI, they are only one aspect of joint function and not a reflection of the overall function. The analysis of children, adolescents and young adults together may have limited kinematic result interpretation, because as previously mentioned walking patterns evolve with age.[12,13]

## 6 | ARE INSTRUMENTAL MEASUREMENTS OF THE STRENGTH CORRELATED WITH 3DGA PARAMETERS?

Stephensen et al[18] evaluated the association of isometric strength with gait patterns in children with PWH. They performed strength measurement with a hand-held dynamometer. Ankle ROM during gait cycle was significantly associated with the muscle strength of the knee extensors ($r = .61$; $P < .001$), ankle plantar flexors ($r = .52$; $P < .005$) and ankle dorsi flexors ($r = .51$; $P < .005$). Peak knee flexion moment during initial double support was inversely associated with muscle strength of knee extensors ($r = -.51$; $P < .005$), ankle plantar flexors ($r = -.43$; $P < .05$) and ankle dorsi flexors ($r = -.46$; $P < .01$). Stephensen et al[5] also studied the correlation between walking and the isokinetic concentric muscle strength measurement of the ankle plantar flexor muscle. In haemophilic children, a significant deficit in isokinetic strength of the ankle plantar flexor was found unlike in typically developed children ($P < .005$). Isokinetic evaluation showed that maximum strength and muscle torque were inversely correlated to peak knee flexion moment during initial double support (respectively, $r = -.64$ and $r = -.61$; $P < .01$), to peak ankle dorsi flexion angle (respectively, $r = -.46$ and $r = -.48$; $P < .05$) and peak knee flexion moment during single support (respectively, $r = -.53$ and $r = -.50$; $P < .05$).

These two studies showed that 3DGA parameters are associated with both isometric and isokinetic strength of the lower limbs. It indicates that modification of the gait parameters is associated with strength deficit even in the absence of arthropathy or patients' complaints.[5] Yet, these results only concerned small groups of children and no study on adults had been performed.

## 7 | IS 3DGA CORRELATED WITH FUNCTIONAL TESTS AND SCORES?

### 7.1 | Children and adolescents

*The six-minute walk test* (6MTW) is a valid tool used in the paediatric population to assess functional capacity in chronic diseases including arthritic ones.[36,37] *Timed up and down stairs* (TUDS) is also used in children to measure functional mobility.[38] Stephensen et al[18] intended to assess if those functional tests were correlated to biomechanical function. They found that 6MTW and TUDS were well associated with some kinematic and kinetic parameters. 6MTW was negatively correlated with peak ankle dorsiflexion angle ($r = -.69$; $P < .001$) and peak knee flexion moment ($r = -0.54$; $P < .001$) during single support. 6MTW was positively linked with ankle range of motion ($r = .75$; $P < .001$). TUDS was positively correlated with peak ankle dorsiflexion angle ($r = .83$; $P < .001$) and peak knee flexion moment ($r = .69$; $P < .001$) during single support, and negatively with ankle range of motion during gait cycle ($r = -.66$; $P < .001$). Both 6MTW and TUDS were negatively correlated with peak ankle dorsiflexion moment during initial double support (respectively, $r = -.73$; $P < .001$ and $r = -.66$; $P < .001$).

These results indicate that alterations of the gait pattern may be easily approached with basic functional tests which could be used to detect walking disturbance. However, these results had been validated in a relatively small group of children with severe haemophilia (n = 21) from 6 to 12 years old and may not be generalized for other groups of age or disease severity.

### 7.2 | Adults

Lobet et al[29] studied the correlation between the functional score and the clinical one in a population of patients with bilateral ankle arthropathy. Foot function was clinically assessed with *Foot Function Index-Revised short form*,[39] especially pain and stiffness subscales. After normalization to speed,[40] only self-reported stiffness was significantly negatively associated with ankle power and peak plantar flexion moment (respectively, $r = -.50$; $P < .05$ and $r = -.48$; $P < .05$). Clinical examination was performed with the examination part of the World Federation of Haemophilia clinical joint score (WFH).[41] No correlation was found between WFH score and 3DGA parameters.

These results are consistent with studies in children showing walking disturbance with normal clinical examination[17] and those in adults showing walking worsening without clinical deterioration.[25] It indicates that 3DGA could be a more sensitive tool than physical examination to detect early walking impairment. Yet, the results are limited by the small size of the group and the heterogeneity concerning overlying arthropathies or joint replacements.

## 8 | DISCUSSION AND PERSPECTIVES

The main purpose of this review was to investigate the interest and the contribution of gait analysis in PWH, and its clinical interest. The population of children is particularly interesting because the signs of the disease appear early in life.[4] Indeed, haemophilia is responsible for joint bleedings, especially in ankles and knees, which in the long-term cause arthropathy and walking disability.[42] However, animal studies have shown that only few joint bleedings are necessary to provide early joint changes.[43] Yet, physical examination and X-rays imaging remain initially normal[5] and MRI uneasily accessible as a routine test. The greatest interest of gait analysis would be to detect early walking changes with a non-invasive and well tolerated examination. In adulthood, this technic may be also useful to help detect walking worsening in patients known to have already arthropathy. Indeed, standard evaluations are not always accurate enough to detect it[44] and walking alterations do not seem to be enough linked to imaging and clinical examination.[8,23,26] Three-dimensional gait analysis is a well-tolerated examination but takes time to realize and needs expensive equipment (optic captors and pressure mats), which limits its possibility of routine use. It is also a non-ecological assessment which requires a gait laboratory whose accessibility is limited to specialized centres. However, 3DGA could be considered an interesting and clinically relevant tool to detect early walking disturbance[15,17] before irreversible joint damage and infra-clinical worsening of the gait,[25] and therefore to adapt regimen of prophylaxis. The use of 3DGA could also appear relevant in the initial assessment and then during the follow-up of PWH. Indeed, it could enable clinicians to have a walking pattern of reference for each patient.

Thanks to our review, we highlighted several 3DGA parameters that seem to be particularly interesting for clinicians in the evaluation of PWH, especially knee joint angles, stance and swing phases (Table 2), which are frequently modified. However, generalizations of these results remain difficult, especially to compare PWH to normal population. Indeed, in the studies, patient groups are small and usually heterogeneous in terms of age and target joints. It certainly results of the rarity of the disease. So, it could be interesting to perform a study with a larger cohort of patients from several referral centres in order to allow subgroup analysis, helping to define clearly the place of 3DGA in the strategy of haemophilia evaluation.

## DISCLOSURES

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

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## REFERENCES

1. White GC, Rosendaal F, Aledort LM, et al. Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII and factor IX of the scientific and standardization committee of the International Society on Thrombosis and Haemostasis. *Thromb Haemost*. 2001;85:560.
2. Bolton-Maggs PH, Pasi KJ. Haemophilias A and B. *Lancet*. 2003;361:1801-1809.
3. Stephensen D, Tait RC, Brodie N, et al. Changing patterns of bleeding in patients with severe haemophilia A. *Haemophilia*. 2009;15:1210-1214.
4. Fischer K, van der Bom JG, Mauser-Bunschoten EP, et al. The effects of postponing prophylactic treatment on long-term outcome in patients with severe hemophilia. *Blood*. 2002;99:2337-2341.
5. Stephensen D, Drechsler WI, Scott OM. Influence of ankle plantar flexor muscle architecture and strength on gait in boys with haemophilia in comparison to typically developing children. *Haemophilia*. 2014;20:413-420.
6. Rodríguez-Merchán EC, Goddard NJ, Lee CA. *Muskuloskeletal aspect of haemophilia*. Vol. 1. 1st ed. Oxford: Blackwell Science; 2000.
7. Hoots WK. Pathogenesis. *Semin Hematol*. 2006;43:S18-S22. https://doi.org/10.1053/j.seminhematol.2005.11.026.
8. Creaby MW, Bennell KL, Hunt MA. Gait differs between unilateral and bilateral knee osteoarthritis. *Arch Phys Med Rehabil*. 2012;93:822-827.
9. Favre J, Erhart-Hledik JC, Andriacchi TP. Age-related differences in sagittal-plane knee function at heel-strike of walking are increased in osteoarthritic patients. *Osteoarthritis Cartilage*. 2014;22:464-471.
10. Hartmann M, Kreuzpointner F, Haefner R, Michels H, Schwirtz A, Haas JP. Effects of juvenile idiopathic arthritis on kinematics and kinetics of the lower extremities call for consequences in physical activities recommendations. *Int J Pediatr*. 2010;2010:835984.

11. Merker J, Hartmann M, Kreuzpointner F, Schwirtz A, Haas J-P. Pathophysiology of juvenile idiopathic arthritis induced pes planovalgus in static and walking condition: a functional view using 3D gait analysis. *Pediatr Rheumatol Online J*. 2015;13:21.
12. Chester VL, Wrigley AT. The identification of age-related differences in kinetic gait parameters using principal component analysis. *Clin Biomech Bristol Avon*. 2008;23:212-220.
13. Chester VL, Tingley M, Biden EN. A comparison of kinetic gait parameters for 3-13 year olds. *Clin Biomech Bristol Avon*. 2006;21:726-732.
14. Lobet S, Detrembleur C, Massaad F, Hermans C. Three-dimensional gait analysis can shed new light on walking in patients with haemophilia. *ScientificWorldJournal*. 2013;2013:284358.
15. Bladen M, Alderson L, Khair K, Liesner R, Green J, Main E. Can early subclinical gait changes in children with haemophilia be identified using the GAITRite walkway. *Haemophilia*. 2007;13:542-547.
16. Suckling LB, Stephensen D, Cramp MC, Mahaffey R, Drechsler WI. Identifying biomechanical gait parameters in adolescent boys with haemophilia using principal component analysis. *Haemophilia*. 2018;24(1):149-155.
17. Stephensen D, Drechsler W, Winter M, Scott O. Comparison of biomechanical gait parameters of young children with haemophilia and those of age-matched peers. *Haemophilia*. 2009;15:509-518.
18. Stephensen D, Taylor S, Bladen M, Drechsler WI. Relationship between physical function and biomechanical gait patterns in boys with haemophilia. *Haemophilia*. 2016;22:e512-e518.
19. Forneris E, Andreacchio A, Pollio B, et al. Gait analysis in children with haemophilia: first Italian experience at the Turin Haemophilia Centre. *Haemophilia*. 2016;22:e184-e191.
20. Zijlstra W, Prokop T, Berger W. Adaptability of leg movements during normal treadmill walking and split-belt walking in children. *Gait Posture*. 1996;4:212-221.
21. Hof AL. Scaling gait data to body size. *Gait Posture*. 1996;4:222-223.
22. Kraan CM, Tan AHJ, Cornish KM. The developmental dynamics of gait maturation with a focus on spatiotemporal measures. *Gait Posture*. 2017;51:208-217.
23. Ganley KJ, Powers CM. Gait kinematics and kinetics of 7-year-old children: a comparison to adults using age-specific anthropometric data. *Gait Posture*. 2005;21:141-145.
24. Dusing SC, Thorpe DE. A normative sample of temporal and spatial gait parameters in children using the GAITRite electronic walkway. *Gait Posture*. 2007;25:135-139.
25. Lobet S, Detrembleur C, Francq B, Hermans C. Natural progression of blood-induced joint damage in patients with haemophilia: clinical relevance and reproducibility of three-dimensional gait analysis. *Haemophilia*. 2010;16:813-821.
26. Lobet S, Hermans C, Bastien GJ, Massaad F, Detrembleur C. Impact of ankle osteoarthritis on the energetics and mechanics of gait: the case of hemophilic arthropathy. *Clin Biomech Bristol Avon*. 2012;27:625-631.
27. Lobet S, Detrembleur C, Hermans C. Impact of multiple joint impairments on the energetics and mechanics of walking in patients with haemophilia. *Haemophilia*. 2013;19:e66-e72.
28. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19:e1-e47.
29. Lobet S, Hermans C, Pasta G, Detrembleur C. Body structure versus body function in haemophilia: the case of haemophilic ankle arthropathy. *Haemophilia*. 2011;17:508-515.
30. Arnold WD, Hilgartner MW. Hemophilic arthropathy. Current concepts of pathogenesis and management. *J Bone Joint Surg Am*. 1977;59:287-305.
31. Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. *Clin Orthop*. 1980;149:153-159.
32. Rodríguez-Merchán EC. Effects of hemophilia on articulations of children and adults. *Clin Orthop*. 1996;328:7-13.
33. Cubukcu D, Sarsan A, Alkan H. Relationships between pain, function and radiographic findings in osteoarthritis of the knee: A cross-sectional study. *Arthritis*. 2012;2012:984060.
34. Brunel T, Lobet S, Deschamps K, et al. Reliability and clinical features associated with the IPSG MRI tibiotalar and subtalar joint scores in children, adolescents and young adults with haemophilia. *Haemophilia*. 2017;24:141-148.
35. Lundin B, Manco-Johnson ML, Ignas DM, et al. An MRI scale for assessment of haemophilic arthropathy from the International Prophylaxis Study Group. *Haemophilia*. 2012;18:962-970.
36. Hassan J, van der Net J, Helders PJM, Prakken BJ, Takken T. Six-minute walk test in children with chronic conditions. *Br J Sports Med*. 2010;44:270-274.
37. Paap E, van der Net J, Helders PJM, Takken T. Physiologic response of the six-minute walk test in children with juvenile idiopathic arthritis. *Arthritis Rheum*. 2005;53:351-356.
38. Zaino CA, Marchese VG, Westcott SL. Timed up and down stairs test: preliminary reliability and validity of a new measure of functional mobility. *Pediatr Phys Ther*. 2004;16:90-98.
39. Budiman-Mak E, Conrad K, Stuck R, Matters M. Theoretical model and Rasch analysis to develop a revised Foot Function Index. *Foot Ankle Int*. 2006;27:519-527.
40. Stoquart G, Detrembleur C, Lejeune T. Effect of speed on kinematic, kinetic, electromyographic and energetic reference values during treadmill walking. *Neurophysiol Clin Neurophysiol*. 2008;38:105-116.
41. Gilbert MS. Prophylaxis: musculoskeletal evaluation. *Semin Hematol*. 1993;30:3-6.
42. Dunn AL. Pathophysiology, diagnosis and prevention of arthropathy in patients with haemophilia. *Haemophilia*. 2011;17:571-578.
43. van Meegeren MER, Roosendaal G, Jansen NWD, Lafeber FPJG, Mastbergen SC. Blood-induced joint damage: the devastating effects of acute joint bleeds versus micro-bleeds. *Cartilage*. 2013;4:313-320.
44. Silva M, Luck JV, Quon D, et al. Inter- and intra-observer reliability of radiographic scores commonly used for the evaluation of haemophilic arthropathy. *Haemophilia*. 2008;14:504-512.


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