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Natural progression of blood-induced joint damage in patients with haemophilia: clinical relevance and reproducibility of three-dimensional gait analysis

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Summary. A major complication in haemophilia is the destruction of joint cartilage because of recurrent intraarticular and intramuscular bleeds. Therefore, joint assessment is critical to quantify the extent of joint damage, which has traditionally been evaluated using both radiological and clinical joint scores. Our study aimed to evaluate the natural progression of haemophiliac arthropathy using three-dimensional gait analysis (3DGA) and to assess the reproducibility of this technique. We hypothesized that the musculoskeletal function was relatively stable in patients with haemophilia. Eighteen adults with established haemophiliac arthropathies were evaluated twice by 3DGA (mean follow-up: 18 ± 5 weeks). Unexpectedly, our findings revealed infraclinical deterioration of gait pattern, characterized by a 3.2% decrease in the recovery index, which is indicative of the subject’s ability to save energy while walking. A tendency towards modification of segmental joint function was also observed. Gait analysis was sufficiently reproducible with regards to spatiotemporal parameters as well as kinetic, mechanical and energetic gait variables. The kinematic variables were reproducible in both the sagittal and frontal planes. In conclusion, 3DGA is a reproducible tool to assess abnormal gait patterns and monitor natural disease progression in haemophilic patients.

Keywords: arthropathy, gait analysis, haemophilia, reproducibility

Introduction

The major complications experienced by patients with haemophilia are recurrent bleeding episodes into the musculoskeletal system, not only into the joints (haemarthrosis) but also into the muscles (haematoma). Destruction of the joint cartilage and irreversible chronic arthropathy are the long-term consequences of repeated haemarthrosis, causing severe and painful functional disability, loss of autonomy and altered quality of life. One of the major goals of medical treatment of haemophilia is to minimize joint structural damage by preventing haemarthrosis. This can be achieved by regular intravenous infusions of plasma-derived or recombinant concentrates of clotting factor VIII or IX, administered as either prophylactic therapy or on-demand therapy.

Musculoskeletal assessment is critical to quantify the extent of articular damage and evaluate therapeutic interventions in patients with haemophilia [1]. This has traditionally been evaluated using both radiological [2,3] and clinical joint scores [4]. Long-term musculoskeletal outcomes have been assessed using these scores, correlating with the intensity of factor replacement therapy [5]. Although the development of radiological and clinical scores signify an invaluable contribution to haemophilia care, these scores exhibit several limitations, such as a lack of psychometric properties (reliability, validity and sensitivity to change) as...
well as their inability to detect early changes in the
haemophilic joint [6,7]. This has prompted the
development of more sensitive scoring systems
based on magnetic resonance imaging [7], as well
as new clinical scores such as the Hemophilia Joint
Health Score [8]. However, as both clinical and
radiological scores are based on the status of
individual joints, they do not integrate the global
and inter-related impact of multiple-joint arthrop-
athy on musculoskeletal function.

An adequate assessment of the musculoskeletal
system should take into account the wide spectrum
of haemophilic arthropathy, which ranges from
small or absent joint damage in young children on
primary prophylaxis to severe disabling arthropathy
in poorly or inefficiently treated patients. Joint
evaluation should be sensitive enough to detect early
articular changes, to minimize the impact of joint
destruction. In patients with established arthropathy,
joint assessment should enable evaluation of the
global functional status, as well as the impact of
limited or diffuse arthropathy on the musculoskeletal
system, to offer a tailored treatment.

Three-dimensional gait analysis (3DGA) is a
promising approach for joint function assessment in
haemophilic patients. 3DGA consists of simulta-
neous analysis of joint kinematic (modelling of body
segment movements), kinetic (study of the force
interactions of the foot with the ground) and
metabolic measurements (calculation of energy con-
sumption). Over the last few decades, 3DGA has
evolved significantly because of advances in com-
puter technology and data analysis techniques [9].
The technique allows for the objective quantification
of motion, permitting the better understanding of
normal and abnormal movement gait patterns. To
date, 3DGA has been widely used in the clinical
decision-making process, and to predict the outcome
of therapeutic interventions in various neurological
or orthopaedic disorders [10–17].

The purpose of this study was primarily to
evaluate the reproducibility of 3DGA in adults with
haemophilia by measuring kinematics, kinetics and
metabolic gait variables. Gait analysis has shown to
be an important tool in determining biomechanical
factors that may influence the outcomes of degener-
ative joint diseases such as osteoarthritis [10]. The
second objective of our study was to estimate the
natural progression of haemophilic arthropathy using
3DGA. We hypothesized that the musculoskeletal
function in patients with haemophilia is relatively
stable. For this reason, musculoskeletal function
should not differ when evaluated by an inter-session
comparison within a short time interval.

Materials and methods

Subjects and experimental design

Eighteen patients with haemophilia regularly fol-
lowed at the Haemophilia comprehensive centre of
the Cliniques Universitaires Saint-Luc, Brussels,
Belgium were enrolled in the study between March
2008 and June 2009. Their characteristics are pre-
sented in Table 1. The study was approved by the
Local Ethical Committee, and all patients gave
written informed consent.

Three-dimensional gait analysis was tested by
comparing gait variables during two sessions per-
formed by the same investigator (S.L.): at baseline
(T0) and after a mean follow-up of 18 ± 5 weeks
(range: 13–33) (T1). At the time of evaluation,
patients had been free of acute joint or muscle
bleeding for the last 30 days. Specific attention was
given to the use of non-steroidal anti-inflammatory
drug (NSAID) prior to 3DGA. Subjects occasionally
using NSAID were instructed to observe a wash-out
period of at least 72 h prior to testing, whereas
those using NSAID daily were told not to interrupt
the treatment. Participants were also asked to
continue their replacement therapy with clotting
factors before and between the 3DGA sessions.

Table 1. Characteristics of the study group.

<table>
<thead>
<tr>
<th>Variables</th>
<th>n = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40 ± 10 (21–60)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81 ± 15 (60–123)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.76 ± 0.06 (1.66–1.87)</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>26.2 ± 4.8 (21–38.8)</td>
</tr>
<tr>
<td>Haemophilia A</td>
<td>17</td>
</tr>
<tr>
<td>Haemophilia B</td>
<td>1</td>
</tr>
<tr>
<td>Severe factor deficiency</td>
<td>16</td>
</tr>
<tr>
<td>Moderate factor deficiency</td>
<td>2</td>
</tr>
<tr>
<td>Clinical assessment</td>
<td></td>
</tr>
<tr>
<td>Ankle arthropathy</td>
<td>18 (2/16)</td>
</tr>
<tr>
<td>(unilateral/bilateral)</td>
<td></td>
</tr>
<tr>
<td>Knee arthropathy without surgery</td>
<td>6 (3/3)</td>
</tr>
<tr>
<td>(unilateral/bilateral)</td>
<td></td>
</tr>
<tr>
<td>Total knee replacement (unilateral/bilateral)</td>
<td>8 (4/4)</td>
</tr>
<tr>
<td>Total hip replacement (unilateral/bilateral)</td>
<td>1 (1/0)</td>
</tr>
<tr>
<td>Elbow arthropathy</td>
<td>13 (3/10)</td>
</tr>
<tr>
<td>(unilateral/bilateral)</td>
<td></td>
</tr>
<tr>
<td>Shoulder arthropathy</td>
<td>2 (0/2)</td>
</tr>
<tr>
<td>(unilateral/bilateral)</td>
<td></td>
</tr>
<tr>
<td>Medical treatment</td>
<td>18 (8/10)</td>
</tr>
<tr>
<td>(prophylaxis/on-demand)</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD (range) for age, weight, height and BMI.
Gait analysis

Gait was assessed using 3DGA which included synchronous kinematic, kinetic, mechanic and metabolic measurements. As this approach generates an extensive amount of variables, data interpretation and understanding may be difficult for a clinician unfamiliar with gait analysis. In an attempt to provide an overview of 3DGA in haemophilic patients, the basic principles are summarized hereafter. Those interested can refer to the technical methodological aspects in the reference list.

A major advantage of 3DGA is its ability to estimate accurately the ‘active’ joint range of movement (ROM) in a ‘real’ weight-bearing condition (kinematic variables) and to provide significant information on the spatial and temporal coordination between lower-limb segments (spatiotemporal parameters). In multiple and severe joint affections such as haemophilia, 3DGA may be used to pinpoint which specific joints or muscles are responsible for the functional deficit.

The sessions began with a rest period, during which the subjects stood on a motor-driven treadmill for static calibration of kinematic and energetic variables. Thereafter, the subjects were asked to walk with neutral running shoes (Kalenji success, Decathlon®, Villeneuve d’Ascq, France) for a few minutes until a steady state was reached and maintained for at least 2 min, to compute energetic variables. Other variables were simultaneously recorded for 20 s and averaged for 10 successive strides. The mean of each value was used for statistical analysis. Mechanical work and energetic variables were calculated for each subject (n = 18), whereas spatiotemporal parameters, kinematics and kinetics were calculated for both legs (n = 36). The subjects walked at a self-selected speed at T0 (1.08 ± 0.19 m s⁻¹). The same speed was imposed at T1 for each subject.

Segmental kinematics were measured using the Elite system (BTS, Garbagnate Milanese, Italy). Six infra-red cameras measured the 3D coordinates of reflective markers placed on specific anatomical landmarks (Fig. 1) allowing computation of the angular displacement [11,18]. Spatiotemporal parameters were assessed thanks to the 3D position data (cadence, step length and percentage of stance/swing phase duration). Four 3D strain-gauge force transducers located under the treadmill recorded the ground reaction forces generated by the body in 3D [19]. Kinematic and kinetic variables provide important information on the type of movement produced using the calculation of joint moment, whereas joint power allows for a better understanding of the muscles’ role in producing and controlling motion [9]. The joint moment and power of the hip, knee and ankle were calculated [11,18,20]. Kinematic and kinetic data were normalized to 100%, 0% corresponding to the initial contact of the foot with the ground.

As suggested by Beeton et al. [1], assessment of lower extremity function is highly relevant in haemophilia care. The traditional clinical and radiological scores tend to document disease consequences at a single joint level, without reflecting the impact on the musculoskeletal function as a whole [5]. Our gait laboratory specifically aims to evaluate the repercussions of segmental abnormalities on global function by calculating more ‘global’ indexes, such as mechanical work, cost, recovery and efficiency. These indexes are likely to be more relevant in the objective assessment of patient problems in performing fundamental tasks such as walking. The total mechanical work (W_{tot}) carried out by the muscles was divided into the external work (W_{ext}) performed to move the centre of body mass (COM) relative to the surroundings, and the internal work (W_{int}) performed to move the body segments relative to the COM [21,22]. The ‘recovery’ was also calcu-

Fig. 1. Three-dimensional gait analysis. (a) The subjects walked with neutral running shoes on a custom-built motorized treadmill mounted on four 3-D strain-gauge force transducers. (b) Infra-red light sources around each camera reflected the retro-reflective markers and generated reconstructed 3D trajectories. The cameras were positioned so that each marker would be seen by two cameras at any given time.
lated. This index is indicative of the efficacy of the gait mechanisms, and defines the subject’s ability to save energy by passively recovering kinetic energy into gravitational potential energy and back again while walking, as does an inverted pendulum [11,23].

The net metabolic cost ($C_{net}$) was calculated as the net oxygen consumption over the walking speed [24]. The efficiency represents the percentage of metabolic cost actually transformed into mechanical energy by muscles and was calculated as the ratio of $W_{tot}$ to $C_{net}$ [10,14,21].

Statistical analysis

**Inter-session reproducibility** To be clinically meaningful, 3DGA assessment must be reproducible. Reproducibility may be defined as agreement (absolute reliability) and reliability (relative reliability) [25].

**Agreement study** Agreement refers to the measurement error and assesses how close the scores are from repeated measurements. In our study, the major potential source of systematic variance was induced by a modification of the subjects’ gait pattern due to the natural progression of joint disease. On the other hand, unsystematic variance consists of natural fluctuation of subjects’ gait pattern as well as potential unreproducibility of the 3DGA itself. The standard error of measurement (SEM) is an agreement measure that provides an estimate of unsystematic variance [26]. As a measure of within-patient variability, it expresses the measurement error in the same units as those of the original measurement. SEM is estimated by taking the square root of the residual variance calculated by an analysis of variance for repeated measures (sigma stat v2.0 for Windows) [12]. It is thus important to note that SEM is independent of the between-subject variability of the variable in the population sample [27]. The coefficient of variation of SEM (SEM%) was also calculated by dividing SEM by the mean of the measurements at T0 and T1, and multiplying by 100. Lower SEM% values reflect lower measurement errors in comparison to higher SEM% values.

The clinician may question how to interpret change score values. Is this change score beyond measurement error that would typically occur during routine 3DGA administration? The minimal detectable change (MDC) represents the safest threshold for identifying statistically detectable individual changes [28]. MDC$_{95}$ was calculated by multiplying SEM by 1.96 and $\sqrt{2}$, where 1.96 is the two-sided tabled Z-value for the 95% confidence interval, and $\sqrt{2}$ is used to account for the variance of two measurements. MDC was expressed as a percentage (MDC%) based on the same principle as SEM%. Lower MDC% values reflect greater responsiveness in comparison to higher MDC% values.

**Reliability study** Reliability reflects the extent to which a measurement instrument differentiates subjects from each other despite the measurement error. The inter-session reliability of 3DGA variables was evaluated by a two-way mixed model absolute agreement intraclass correlation coefficient (ICC) (spss v16.0 for windows; SPSS Inc., Chicago, IL, USA) according to Shrout and Fleiss in which an ICC ≥0.75 indicates excellent reliability, between 0.75–0.40 fair to good reliability, and <0.40 poor reliability [29].

**Inter-session comparison** To evaluate the natural progression of gait over time, comparison of 3DGA variables across the two time intervals was performed using a paired t-test (sigma stat v2.0 for Windows). For non-Gaussian continuous variables, Wilcoxon’s signed-rank non-parametric test for paired variables was used. A P value of 0.05 or less was considered statistically significant.

Results

**Inter-session reproducibility**

The agreement and reliability of the study results are presented in Table 2. Spatiotemporal variables showed the least measurement error, with SEM% inferior to 3%, and excellent reliability (ICC values between 0.84 and 0.96). The reproducibility of kinematics ranged from poor to excellent. In general, kinematic ROM variables were highly reproducible for the ankle, knee and hip in both the sagittal and frontal planes. The SEM% were inferior to 13%, and ICC values were comprised between 0.79 and 0.94, except for the ankle maximum dorsiflexion at loading response (SEM% = 17%, ICC = 0.72). Kinematic variables in transverse plane for all the lower-limb joints were least reproducible. Pelvic kinematics exhibited generally poor reproducibility, except for the frontal plane which showed moderate agreement and reliability (SEM% = 19%, ICC = 0.65). The reproducibility of joint position in sagittal plane at heel strike was poor for the ankle and knee, and moderate for the hip. With regard to kinetic variables, agreement at the ankle and knee levels was generally satisfactory, with SEM% comprised between 12% and 16%, except for the hip maximum flexion moment at early swing phase and the hip
Table 2. Reproducibility study of three-dimensional gait analysis (3DGA) variables and paired comparison between the two periods T0 and T1.

<table>
<thead>
<tr>
<th>Spatiotemporal parameters (n = 36)</th>
<th>Agreement</th>
<th>Reliability</th>
<th>Paired comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEM</td>
<td>SEM%</td>
<td>MDC95</td>
<td>MDC95%</td>
</tr>
<tr>
<td>Cadence (step/min)</td>
<td>2.99</td>
<td>2.8</td>
<td>8.3</td>
</tr>
<tr>
<td>Step length (metre)</td>
<td>0.02</td>
<td>2.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Stance phase duration (% gait cycle)</td>
<td>0.48</td>
<td>0.7</td>
<td>1.3</td>
</tr>
</tbody>
</table>

| Kinematic (n = 36) | | | | |
| Ankle dorsiflexion at heel strike (°) | 2.71 | 32.9 | 7.5 | 91.2 | 0.66 | 8.7 ± 4.8 | 7.8 ± 4.5 | 0.157 |
| Ankle maximum flexion at loading response (°) | 1.70 | 17.0 | 4.7 | 47.0 | 0.72 | 9.2 | 9.7 | 0.35 |
| Ankle sagittal ROM at push-off phase (°) | 1.24 | 8.2 | 3.4 | 22.7 | 0.94 | 15.1 ± 4.9 | 15.3 ± 4.8 | 0.71 |
| Ankle transversal ROM (°) | 1.92 | 23.2 | 5.3 | 64.2 | 0.71 | 12.0 | 12.2 | 0.229 |
| Ankle average transversal position (°) | 3.24 | 17.7 | 9.0 | 48.9 | 0.74 | 32.0 ± 9.5 | 31.2 ± 9.8 | 0.597 |
| Knee flexion at heel strike (°) | 4.43 | 53.9 | 12.3 | 149.3 | 0.74 | 7.3 ± 8.7 | 9.1 ± 8.9 | 0.087 |
| Knee maximum flexion at loading response (°) | 1.95 | 18.1 | 5.4 | 50.2 | 0.91 | 15.1 ± 4.9 | 15.3 ± 4.8 | 0.71 |
| Knee ROM in swing phase (°) | 2.92 | 52.5 | 8.1 | 14.3 | 0.91 | 32.0 ± 9.5 | 31.2 ± 9.8 | 0.597 |
| Hip flexion at heel strike (°) | 4.89 | 15.5 | 13.6 | 43.0 | 0.74 | 7.3 ± 8.7 | 9.1 ± 8.9 | 0.087 |
| Hip sagittal ROM (°) | 2.66 | 12.3 | 3.7 | 34.2 | 0.82 | 10.9 ± 3.1 | 10.7 ± 3.1 | 0.431 |
| Hip frontal ROM (°) | 3.10 | 19.7 | 8.6 | 54.6 | 0.59 | 15.3 ± 4.8 | 15.2 ± 4.9 | 0.14 |
| Hip transversal ROM (°) | 1.91 | 57.9 | 5.3 | 160.6 | 0.02 | 2.9 | 2.8 | 0.677 |
| Pelvic sagittal ROM (°) | 1.37 | 19.1 | 3.8 | 52.9 | 0.65 | 7.4 ± 2.4 | 6.9 ± 2.2 | 0.172 |
| Pelvic frontal ROM (°) | 2.79 | 43.7 | 7.7 | 121.1 | 0.47 | 5.4 | 5.5 | 0.677 |
| Pelvic transversal ROM (°) | 1.37 | 19.1 | 3.8 | 52.9 | 0.65 | 7.4 ± 2.4 | 6.9 ± 2.2 | 0.172 |

| Kinetic (n = 36) | | | | |
| Ankle max plantarflexion moment at push-off phase (N m kg⁻¹) | 0.14 | 13.6 | 0.39 | 37.7 | 0.70 | 1.07 ± 0.22 | 1.02 ± 0.30 | 0.149 |
| Knee max extension moment at loading response (N m kg⁻¹) | 0.06 | 12.3 | 0.18 | 34.2 | 0.74 | 32.0 ± 9.5 | 31.2 ± 9.8 | 0.597 |
| Hip max extension moment at early loading response (N m kg⁻¹) | 0.06 | 12.1 | 0.16 | 33.4 | 0.47 | 0.47 ± 0.14 | 0.47 ± 0.12 | 0.902 |
| Hip max flexion moment at early swing phase (N m kg⁻¹) | 0.06 | 24.0 | 0.16 | 66.5 | 0.64 | 0.25 ± 0.09 | 0.22 ± 0.10 | 0.023* |
| Ankle max power at push-off phase (W kg⁻¹) | 0.30 | 15.6 | 0.84 | 43.3 | 0.88 | 1.93 | 1.75 | 0.073 |
| Knee max eccentric power at swing phase (W kg⁻¹) | 0.19 | 15.1 | 0.53 | 41.7 | 0.79 | 1.17 | 1.28 | 0.075 |
| Hip max positive power of extensors at early loading response (W kg⁻¹) | 0.11 | 21.4 | 0.29 | 59.2 | 0.74 | 0.47 ± 0.23 | 0.52 ± 0.20 | 0.092 |
| Hip max positive power of flexors at early swing phase (W kg⁻¹) | 0.02 | 7.6 | 0.04 | 21.0 | 0.67 | 0.22 ± 0.10 | 0.20 ± 0.10 | 0.129 |

| Mechanical work/Energetics (n = 18) | | | |
| External work (J kg⁻¹ m⁻¹) | 0.02 | 7.2 | 0.05 | 20.0 | 0.80 | 0.24 ± 0.04 | 0.25 ± 0.04 | 0.185 |
| Internal work (J kg⁻¹ m⁻¹) | 0.02 | 9.4 | 0.06 | 26.2 | 0.81 | 0.24 ± 0.05 | 0.24 ± 0.06 | 0.686 |
| Total work (J kg⁻¹ m⁻¹) | 0.02 | 5.0 | 0.07 | 13.9 | 0.84 | 0.48 ± 0.06 | 0.50 ± 0.07 | 0.184 |
| Recovery (%) | 2.19 | 34.7 | 6.1 | 9.4 | 0.90 | 65.4 ± 8.0 | 63.3 ± 7.9 | 0.01* |
| Cost (J kg⁻¹ m⁻¹) | 0.21 | 8.0 | 0.59 | 22.2 | 0.92 | 2.64 ± 0.71 | 2.65 ± 0.71 | 0.837 |
| Efficiency (%) | 2.17 | 11.0 | 6.0 | 30.4 | 0.87 | 19.6 ± 5.6 | 20.0 ± 6.0 | 0.647 |

SEM, standard error of measurement; SEM%, coefficient of variation of the SEM; MDC95, minimal detectable change using a 95% confidence interval; MDC95%, coefficient of variation of the MDC95; ICC, intraclass correlation coefficient; ROM, range of movement. *P < 0.05; **P < 0.005.

1Positive and negative kinematic transversal values represent respectively internal and external rotation.

1Values are mean ± SD or median [P25;P75].

1Not meaningfully interpretable.
maximum positive power of extensor at early loading response, which showed SEM% superior to 20%. The reproducibility of mechanical and energetic variables was good to excellent, with SEM% inferior to 11% and ICC ranging from 0.80 for $W_{ext}$ up to 0.92 for the cost. The recovery index was most likely the most stable mechanical variable, with a SEM% of approximately 3% and an ICC of 0.90.

Calculation of the MDC$_{95}$ and MDC$_{95\%}$ provides a frame of reference for judging change for a single 3DGA variable. For example, the MDC value for the $W_{tot}$ indicates that for a same patient evaluated twice, a change of 0.07 J kg$^{-1}$ m$^{-1}$ is likely to reflect a true change. Spatiotemporal parameters had the lowest MDC% values, indicating that compared with baseline, a change of 2% in stance phase duration and 8% in step length and cadence can be considered significant changes. Mechanical and energetic variables showed MDC% comprised between 10% and 30%. Kinematic ROM in sagittal and frontal planes had acceptable responsiveness, with MDC$_{95\%}$ comprised between 14% and 34%. On the contrary, the other kinematic variables were not sensitive to change, with MDC$_{95\%}$ superior to 40%. As some variables were not normally distributed, their MDC$_{95}$ and MDC$_{95\%}$ were not meaningful.

**Inter-session comparison**

The spatiotemporal variables changed in a very discrete manner as the mean stance phase duration adopted by patients increased from 65.2 ± 1.5% of gait cycle at T0 to 65.6 ± 1.5% at T1 ($P = 0.002$). A small and almost significant increase in step cadence was observed (106.2 ± 7.3 vs. 107.5 ± 8.0, $P = 0.058$). Contrary to ankle ROM, the knee and the hip increased their movement magnitude in the sagittal plane. The knee ROM during the swing phase increased from 55.1 ± 10.7° at T0 to 58.0 ± 11.9° at T1 ($P < 0.001$), while the hip increased from 42.1 ± 6.1° to 43.3 ± 5.8° ($P = 0.076$). A trend towards change in joint power variables was also noted with time. A decrease in maximum ankle power at push-off phase (median value 1.93 W kg$^{-1}$ at T0 vs. 1.75 W kg$^{-1}$ at T1, $P = 0.073$), an increase in knee eccentric power at swing phase (median value −1.17 W kg$^{-1}$ at T0 vs. −1.28 W kg$^{-1}$ at T1, $P = 0.075$) and an increase in hip positive power at early loading response (0.47 ± 0.23 W kg$^{-1}$ at T0 vs. 0.52 ± 0.20 W kg$^{-1}$ at T1, $P = 0.092$) were observed. A slight decrease in hip maximum flexion moment at early swing was also observed (−0.25 ± 0.09 N m kg$^{-1}$ at T0 vs. −0.22 ± 0.10 N m kg$^{-1}$ at T1, $P = 0.023$).

With regard to the mechanical and energetic variables, a single but important change observed was related to the recovery index. An unexpected deterioration of the pendulum-like mechanism of gait was defined by a 2.1% decrease in the recovery index (65.4 ± 8.0% at T0 vs. 63.3 ± 7.9% at T1, $P = 0.01$), reflecting a 3.2% impairment in regard to the baseline value at T0.

**Discussion**

This study describes the use of 3DGA to assess the global musculoskeletal function in adults with haemophilia. Our results report a good reproducibility in regard to spatiotemporal parameters, kinematic (sagittal and frontal planes), kinetic, mechanical and energetic gait variables. The inter-session comparison revealed an unexpected infraclinical deterioration of gait pattern over a short time period of 18 weeks.

To optimize haemophilia treatment strategies, an accurate musculoskeletal function assessment is essential to diagnose haemophilic arthropathy, initiate strategies to treat or prevent progression of joint disease, assess treatment response and compare outcomes of various treatment strategies [30]. Haemophilic joint status is traditionally evaluated using several clinical [4,7] or radiographical scoring systems [2,3,6]. Nevertheless, these scores are not sensitive enough to detect early changes in patients with little or absent joint damage as well as changes in patients with established arthropathy [3,6]. The summation of clinical or radiological individual joint scores may not be sensible, as the summation of ordinal figures does not provide an actual magnitude [26]. In conclusion, there is a lack of appropriate instruments for accurately measuring global musculoskeletal function in patients with haemophilia.

**Gait analysis as a joint assessment tool in patients with haemophilia**

Most likely because of recruitment difficulties, relatively few studies have focused on gait disorders in patients with haemophilia. Using ultrasound motion analysis allowing for kinematic measurement of the tibiotal and subtalar joints, Seuser et al. [31] reported the first study evaluating the efficacy of a conservative orthopaedic treatment in patients with ankle arthropathy. More recently, Stephensen et al. [32] published the first 3DGA study integrating both kinematic and kinetic variables in children with
haemophilia. Although focused only on the sagittal plane, the authors reported significant changes in kinematics and kinetics in children with haemophilia in comparison with age-matched healthy controls. Their results suggested that early biomechanical changes were present in children with a history of target joint, while lower-limb joint function was more impaired than the current clinical evaluation suggested, confirming previous observations reported by Bladen et al. [33]. Using a simplified gait analysis system, the authors reported abnormalities in spatiotemporal parameters in asymptomatic children with haemophilia and additional significant differences in children with established arthropathy.

**Evaluation of natural progression of haemophilic arthropathy by gait analysis**

Progression of 3DGA variables over time has never been evaluated in patients with haemophilia. We hypothesized that musculoskeletal function in patients with haemophilia would remain stable over our relatively short interval of 18 weeks. This hypothesis was supported by the fact that the patients were evaluated in the same medical and experimental conditions. Unexpectedly, the comparison of 3DGA across the two time intervals revealed small but significant changes in some gait variables, revealing infraclinically deterioration of gait pattern over time. In addition to the significant changes, non-significant changes with a P value close to 0.05 should also be considered as they may provide valuable information. At single joint level, 3DGA showed a minor but highly significant 3° increase in knee ROM during swing phase, and a trend towards joint moment and power increases at the hip and the knee levels. All of the 18 subjects suffered from ankle arthropathy (Table 1), and a deterioration of ankle function (characterized by a tendency towards power decrease at the propulsive phase of walking) was observed over time. These changes may be accounted for by an adaptation of the knee and hip to ankle function deterioration. The most relevant change overall was a 2.1% decrease in recovery. The efficacy of gait’s mechanisms can be quantified by the recovery index, which represents the energy transferred between potential and kinetic energies while walking. Abnormal movements of body segments due to the lowest level gait disorders, such as musculoskeletal disorders, influence the motion of the COM while walking. To the best of the authors’ knowledge, only few studies have assessed mechanical work while walking, enabling the calculation of the recovery index [14]. As suggested by Detrembleur et al. [15], our findings imply that the calculation of the recovery index, and by extension the study of 3D motion of the COM, may be an integrative indicator of the progression of gait pattern under pathological conditions.

**Reproducibility of gait analysis in patients with haemophilia**

Reproducibility studies of assessment tools are necessary to ensure that the error involved in measurement is small enough to allow for the detection of actual changes [25]. The reproducibility of 3DGA has been primarily based on studies on healthy subjects [34] with little exploration performed in patients’ populations. To date, no study has evaluated the reproducibility of 3DGA in patients with haemophilia.

This study supports and extends the results of previous work, stressing the high reliability of mechanical and energetic variables. Similar recovery, cost and efficiency ICC values have previously been reported in healthy children, children with cerebral palsy and adult patients after stroke [13,16]. In addition, we found excellent reliability of spatiotemporal parameters, consistent with similar ICC values reported in Alzheimer’s disease patients [17]. Concerning joint kinematic, our study confirmed the same trends as reported in the review by McGinley et al. [35], namely a high reliability of ankle, knee and hip kinematic in the sagittal and frontal planes, and a poor reliability for the hip in the transverse plane, and pelvis in the three planes. The poor reliability of pelvic kinematic in the three planes along with the lower-limb kinematic in the transverse plane was reported in a previous study [36]. With regard to the joint moments and powers, the ankle power at push-off phase was fairly reproducible, whereas the power generated by the knee and the hip showed slight variation. Reliable reports did not always coincide with agreement results. Despite excellent reliability scores (ICC = 0.91), the knee maximum flexion at loading response exhibited moderate agreement, with a SEM% ≈ 18%. Reliability parameters are dependent on between-subjects variance. The great amount of homogeneous values in the population sample for the variable might explain the lower ICCs, whereas heterogeneity in the sample would have resulted in higher ICCs.

Calculation of error magnitude with the mean of MDC enables the minimization of the risk of over-interpreting small differences for a same subject evaluated twice as meaningful, and allows us to have
greater confidence that a real improvement/deterioration exceeds the measurement error [35]. The calculation of MDC% suggests that some 3DGA variables (spatiotemporal parameters, kinematic ROM in sagittal plane, mechanics and energetic) are better suited for detecting real changes in gait pattern in haemophilia subjects than other 3DGA measures (kinematic in transverse plane and joint position at heel strike). Whether the MDC values are sufficiently low will be related to the magnitude of the expected intervention effect size context. Surgical intervention such as a knee replacement is likely to induce changes superior to MDC in numerous gait variables, whereas more conservative approaches (such as use of NSAID) could induce actual but more subtle gait modifications, resulting in differences inferior to MDC values. We calculated the MDC with a confidence interval of 95%; however, an MDC90 or less could be selected, depending on the precision needed for the score estimate. As a result of its capacity, to detect small but significant changes even in relatively short intervals, 3DGA appears to be a powerful tool to assess abnormal gait patterns in cohort studies. Our findings, however, need to be confirmed using longer follow-up and larger population samples.

Our overall strong reproducibility results may be explained to some extent by the strictly similar medical and experimental conditions that the subjects were evaluated under, at the same spontaneous treadmill speed and the high number \((n = 10)\) of gait cycles averaged for each 3DGA trial. Some of the error measurements were probably inherent to our patient population. Poor results of pelvic kinematic may be explained to some extent by the difficulty in finding pelvic and femoral anatomical landmarks in some of our overweight subjects. The overall poor reproducibility of transverse plane kinematic may be explained by a potential inconsistency in the alignment of reflective markers on the thighs and legs.

Our study has some limitations. The choice of a mean time interval of 18 weeks was practical: 3DGAs were performed the same day as the other medical consultations. Ideally, a 3DGA reproducibility study would include between-session intervals that are far apart, to minimize bias effects such as memorization of the reflective marker position. In contrast, longer time periods as adopted in our study increase the possibility that real change has occurred within the 3DGA interval, potentially introducing disease progression bias [35]. Inter-session comparison confirmed a systematic error induced by natural disease progression. Nevertheless, we decided to perform the reproducibility study for two main reasons. First, the systematic error induced by disease progression was not taken into account in the agreement study, as SEM calculation relies on the residual variance, thus including only unsystematic factors in contrast with ‘real’ change. Moreover, as suggested by inter-session comparison results, the systematic changes due to disease progression were actual although subtle and should consequently induce only a slightly underestimation of ICCs. Second, the principal aim of our reproducibility study was not to focus on raw reproducibility scores, but rather to establish a hierarchy of 3DGA variables to be considered either with confidence or distrust for future clinical research.

**Conclusion**

To our knowledge, this is the first study to document the natural progression of haemophilic arthropathy. Using a population of haemophilic adults with established arthropathies, our results revealed an unexpected infraclinical deterioration of gait pattern over a short-time period, as well as a tendency towards segmental joint adaptation in response to progressive joint function deterioration. Clinical gait analysis is therefore a powerful tool to assess abnormal gait patterns and the effects of disease progression in patients with haemophilia. Gait analysis is sufficiently reproducible in regard to spatio-temporal parameters, kinetic, mechanical and energetic gait variables. The kinematic variables were only reproducible for the ankle, knee and hip ROM in the sagittal and frontal planes.

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**Disclosures**

The authors state that they have no conflict of interest.

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