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Evaluation of gait in Duchenne Muscular Dystrophy: Relation of 3D gait analysis to clinical assessment

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Abstract

Walking ability in Duchenne Muscular Dystrophy (DMD) deteriorates progressively until complete loss of the function. Interventions aimed at maintaining ambulatory ability relies on accurate clinical-based scores and evaluations of walking. This kind of assessment has intrinsic limitations. A 3D optoelectronic system could provide elements useful for the functional evaluation of patients with DMD. Nineteen boys with DMD were evaluated using the 6-Minutes Walking Test, North Star Ambulatory Assessment and 3D gait analysis. Participants' gait parameters were compared to those of an age-matched control group and correlated with standard clinical scores. Seventeen kinematic variables differed between DMD and control groups. Strong correlations with North Star Ambulatory Assessment were found for stride width, gait velocity and ankle angles on the sagittal plane. The 6-Minutes Walking test did not correlate with investigated kinematic variables but showed a correlation with North Star Ambulatory Assessment. Our data support the reported DMD gait pattern characterized by increased anterior pelvic tilt and ankle plantar flexion. The stride width and ankle kinematics emerged as the main representative gait parameters of DMD global ambulatory status. Although preliminary, our findings suggest that 3D gait analysis may provide useful objective and accurate parameters reflecting the functional ability of individuals with DMD.

Keywords: Duchenne Muscular Dystrophy; North Star Ambulatory Assessment; 6-minutes walking test; 3D gait analysis; Gait pattern; Kinematics.

1. Introduction

Duchenne Muscular Dystrophy (DMD) is a severe X-linked degenerative muscular disorder that affects approximately 1:3500 males born alive [1–3]. DMD is caused by mutations in the gene coding for dystrophin, a muscle cytoskeletal membrane protein. The loss of dystrophin function causes progressive loss of functional muscle mass and replacement with fibro-fatty tissue [4]. The main consequences of DMD are a decline in muscle strength and motor function. Classically, the manifestation of the disease is an early loss of the ambulation. In the second decade of life, orthopedic, respiratory and cardiac complications occur causing premature death in the third or fourth decade of life [4].

The alteration of functional motor patterns includes gait and posture changes and musculoskeletal deformities, which contribute to the disability, poor quality of life and comorbidity of patients with DMD [1]. Therefore, the maintenance of ambulatory ability is one of the main rehabilitative goals in this population [5], in order to postpone physical dependency and orthopedic complications [4]. In this perspective, evaluation of the motor parameters in patients with DMD is very important. Currently, it relies on different clinically-based measurement tools. In particular, ambulant boys are commonly assessed by validated outcome measures such as the 6-minutes walking test (6MWT) [6]. 6MWT

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is a clinical scale originally developed to evaluate cardiac and respiratory insufficiency and subsequently adapted for the pediatric population with DMD to quantify the walking endurance. However, 6MWT has only been validated for children older than 5 years [7,8]. Another specific functional scale widely used in clinical practice is the North Star Ambulatory Assessment (NSAA). It is a one-dimensional, disease-specific scale that also includes timed items and the Hammersmith Motor Ability Scale (HMAS) [7,9]. The NSAA has been widely used to measure the ambulatory function of boys with DMD [10,11] and has been recently adapted for use with children above the age of three [9,12]. Both 6MWT and NSAA measures fit the construct for DMD and reflect clinically relevant activities, such that they are now routinely used in trials and observational longitudinal studies [7,10,11,13–15]. Evidence suggests that, for the evaluation of subjects with DMD, the 6MWT has the advantage of being an integrated global measure of ambulatory function. In fact, the 6MWT assesses the lower extremity strength, biomechanical inefficiencies, endurance, and cardiorespiratory status [16,17]. However, it is limited by the learning effect, inter- and intra-personal variability, the impact of age at baseline and the interference of a growth effect, as well as the lack of long-term data for assessment in case of loss of ambulation [18].

Quantitative 3D gait analysis by optoelectronic systems allows kinematic and kinetic assessment of walking pattern, and also represents overall gross motor skill [19]. Although widely used in the population with DMD, findings from different studies are not univocal and homogeneous [20]. Indeed, several discrepancies emerged in main joint kinematics of patients when compared to typically-developed age-matched controls [5,21–26]. Goudriaan et al. [20] recently reviewed the wide number of variables obtained from 3D gait analysis that differentiates the gait of children with DMD from typically-developed individuals. In particular, the reduced stride length and increased step width were indicated [24] as significant spatiotemporal parameters in this population. Likewise, the main kinematic abnormalities were increased anteversion of the pelvis, increased excursion range of movements of the knee, and increased plantar flexion of the ankle during the whole gait cycle, with a reduction of dorsiflexion peak in both swing and stance phases [5,21,24,25]. In the field of neurological disorders, 3D gait analysis is now considered as a potential source of biomarkers, tracking disease progression and predicting prognosis of patients, fundamental for improving the overall clinical management [27–29].

In this exploratory study, we extensively analyzed the kinematic gait parameters of a group of boys with DMD compared to an age-matched typically-developed group. We thus attempted to explore the use of 3D gait analysis for supporting the routine assessment of patients with DMD. Specifically, we aimed to determine if altered spatiotemporal and kinematic gait features are related to the outcomes of the 6MWT and the NSAA in a group of children with DMD, thereby providing a more objective and accurate means of assessing disease progression in this population.

2. Materials and methods

Data were collected from one single center, the Unit of Neuromuscular Disease and Neurorehabilitation at the Bambino Gesù Children's Hospital. For this study, we screened 20 male subjects with genetically-confirmed DMD diagnosis. All subjects were able to walk independently. Average duration of the disease was calculated from the onset of the first symptoms reported by the parents to the time of the first evaluation. All patients included in the analysis were treated according to the standards of care [30] and comprised glucocorticosteroids (GC) – deflazacort therapy with, administered daily in 10 patients and as an alternate day regimen in the other 10 patients at the same dosage of 0.9 mg/kg/day. The differences of the selected variables between participants who received the pharmacological treatment on a daily regimen and those on an alternate-day regimen were analyzed to establish whether the regimen of pharmacological treatment can affect the results of the study. Seventeen healthy age-matched male children (mean age: 8.7 ± 3.4 years range: 3–14 years) were recruited as a control group (Ctrls).

An overview of demographics and clinical scores is given in Table 1. Prior to participation, all subjects were informed about the purpose of the study and its procedures, and written informed consent was obtained.

2.1. 3D gait analysis

3D gait analysis was carried out for both participants with DMD and those included in the Ctrls by an eight-camera motion capture system (Vicon MX, UK) with sampling rates set at 200 Hz. Each walking trial was video recorded with two high definition cameras (one in front and one at the side of the child) set at 100 Hz sample rate to assist clinical interpretation of data. Three consistent gait cycles were collected for each evaluation. Gait analysis was conducted with patients walking barefoot at their own self-selected speed on a 10×3 m walkway. Thirty-five spherical (15 mm diameter) reflective markers were located on anatomical landmarks of the subjects as indicated by the Plug-in-Gait protocol [28,29,31] in order to reconstruct a full-body kinematic and kinetic model. Kinematic temporal series were normalized to the stride duration. Walking velocity, stride length and stride width were normalized to leg length [32].

From 3D gait analysis, we selected 29 variables (Table 2) concerning spatiotemporal parameters and the lower limb kinematics of gait. Variables were selected based on recent literature review [20] and on a previous study focused on clinical gait classification of this population [5]. The purpose of this selection was to detect the main characteristics of patients' gait pattern.

During every gait cycle analysis, data concerning the left and right sides of the patient's body were extracted separately. As gait deviations are reported to be symmetric between both lower limbs in the population with DMD [25], data extracted for each variable for the right and the left sides were averaged

Table 1
Participants descriptions.

	DMD Group			Ctrls Group			Difference p-val
	Mean (SD)	Median	Range	Mean (SD)	Median	Range	
Age (years)	10.2 (2.7)	11.0	10.2	8.7 (3.4)	8.0	11.0	0.145
Weight (Kg)	35.9 (9.0)	36.8	31.0	34.8 (13.0)	34.3	44.3	0.769
Height (cm)	129.7 (10.9)	127.0	38.0	133.5 (18.7)	135.0	70.0	0.465
Leg Length (cm)	67.9 (6.6)	67.0	24.0	73.7 (12.3)	76.0	44.0	0.096
Age of onset (years)	3.9 (1.7)	4.0	7.0	/	/	/	/
Duration (years)	6.3 (2.8)	5.6	12.2	/	/	/	/
Age of therapy (years)	5.1 (1.3)	5.0	5.5	/	/	/	/

Descriptive statistics of age, pathology age of onset and duration, years of therapy consumption, and anthropometric measures of DMD participants and control group (Ctrls). Comparison between age and anthropometric characteristics of DMD and Ctrls groups.
#the variable was not normally distributed in at least one of the two groups.
*p-value < 0.05 compared between DMD and Ctrls.
**p-value < 0.0001 compared between DMD and Ctrls. /: no data for the cell.

Table 2
Description of spatiotemporal parameters and kinematic variables obtained from 3D gait analysis and involved in this study.

Gait parameters	Description
Spatio-temporal Parameters	
Normalized walking speed $(v * (\sqrt{} (g * L))^{-1})$	Mean velocity of progression normalized to account for the subject's leg length and gravitational acceleration
Normalized stride length (m / L)	Length of the single cycle normalized to the subject's leg length
Stride time (s)	Duration of the single gait cycle
Cadence (step / s)	Number of steps per minute
Normalized stride width (m / L)	Transversal distance between the right and left foot normalized to the subject's leg length
Double support time (s)	Time in which both feet are in contact with the floor during one gait cycle
Kinematics (degrees)	
Pelvis tilt mean angle	Mean value of pelvis movement on the sagittal plane
Pelvis tilt ROM	Range of Motion of the pelvis movement on the sagittal plane
Pelvis tilt angle at IC	Value of pelvis angle on sagittal plane at the initial contact
Pelvis obliquity ROM	Range of Motion of the pelvis on the frontal plane
Pelvis obliquity angle at IC	Value of pelvis angle on frontal plane at the initial contact
Pelvic rotation ROM	Range of Motion of the pelvis on the transversal plane
Hip flex-ext ROM	Range of motion of the hip on the sagittal plane
Hip add-abd mean angle	Mean value of hip movement on the frontal plane
Hip max flex	Maximum of hip flexion on sagittal plane
Hip max ext	Maximum of hip extension on sagittal plane
Knee flex-ext ROM	Range of motion of the knee on the sagittal plane
Knee flex at IC	Value of knee angle on sagittal plane at the initial contact
Knee max flex in stance	Maximum of knee flexion on sagittal plane in stance phase
Knee max flex in swing	Maximum of knee flexion on sagittal plane in swing phase
Knee max ext in stance	Maximum of knee extension on sagittal plane in stance phase
Ankle flex-ext mean angle	Mean value of ankle movement on the sagittal plane
Ankle flex-ext ROM	Range of motion of the ankle on the sagittal plane
Ankle flex at IC	Value of ankle angle on sagittal plane at the initial contact
Ankle max dorsiflex in stance	Maximum of ankle dorsiflexion on sagittal plane in stance phase
Ankle max dorsiflex in swing	Maximum of ankle dorsiflexion on sagittal plane in swing phase
Ankle max plantar flex	Maximum of ankle plantar flexion on sagittal plane
Foot progress rotation mean angle	Mean value of foot progression angle on the transversal plane
Foot progress rotation ROM	Range of motion of foot progression angle on the transversal plane

Abbreviation; in order of appearance: v = walking speed expressed in meters per seconds; g = gravitational acceleration expressed in meters per (seconds square); L = leg length expressed in meters; m = meters; s = seconds; ROM = Range of Motion; IC = Initial Contact; flex = flexion; ext = extension; add = adduction; abd = abduction; max = maximum; dorsiflex = dorsiflexion; plantar flex = plantar flexion.

together. In this way numeric values were obtained for each variable for each patient.

2.2. NSAA and 6MWT

The North Star Ambulatory Assessment (NSAA) was performed for all the participants with DMD. The scale consists of 17 items from standing to running. For each item a score is given on a three-point scale from 0 to 2. The score 0 corresponds to the inability to complete the item independently. Score 1 is assigned if the item is completed independently but with changes in resolution pattern. Score 2 corresponds to completion of the item without obvious changes in the way it is performed. The scores are added

together to obtain an overall value of the motor function (maximum score: 34). A higher score corresponds to a higher level of functional ability [33]. Thirteen subjects with DMD performed the 6MWT, according to the American Thoracic Society guidelines [6]. The remaining six patients with DMD were not able to perform the 6MWT due to behavioral problems. Both clinical assessments were only performed with patients with DMD in order to get a comparison with 3D gait analysis.

2.3. Statistical analysis

This analysis was carried out using the statistical software IBM SPSS Statistics 25 and MathWorks MATLAB R2018a. Normality of all interval or ratio variables (subjects' age, weight, height, leg length, kinematic and spatiotemporal parameters, NSAA, 6MWT) was tested with the Shapiro–Wilk test. The Lavene test was used to test variance homogeneity of all investigated variables. For each mentioned kinematic and spatiotemporal variable, mean values of patients and controls were compared using Student's *t*-test for normally distributed variables which showed homogeneous variance between groups. The Welch *t*-test was run for variables with non-homogeneous variance. The Mann-Whitney test was used for non-normally distributed variables. Threshold for significance for the aforementioned comparison has been assumed as $\alpha = 0.05$. The Pearson correlation coefficient was calculated for the correlation between clinical assessment and 3D gait analysis when the variables were normally distributed. Spearman's rank correlation was used for non-normally distributed variables. The Bonferroni correction for multiple comparisons was applied after correlation analyses. Twenty-nine comparisons were made, so the significant threshold for the correlation analysis was set to $\alpha = 0.002$ according to the Bonferroni correction ($\alpha = 0.05$ divided by 29 comparisons).

3. Results

One of the candidates was excluded due to previous Achilles tendon lengthening surgery, reducing the number of participants to 19. Average age for the selected participants with DMD was 10.2 ± 2.7 years; range: 6.3 – 16.5 years. Average duration of the disease was 6.3 ± 2.8 years; range 2.3 – 14.5. Mean age of children included in Ctrls group was 8.7 ± 3.4 years; range 3–14 years. Age and anthropometric parameters of subjects with DMD were not different from Ctrls (Table 1).

Statistical analysis showed that the selected kinematic and spatiotemporal variables do not differ between subjects following cortisone therapy on a daily regimen and subjects on an alternate-day regimen. Results obtained from kinematic analysis showed a significant difference between subjects in the DMD group and Ctrls in seventeen variables, see Table 3. The normalized walking speed was reduced in patients compared to Ctrls (*p:* 0.009). Coherently, cadence and normalized stride length of boys with DMD were reduced compared with Ctrls, but these parameters did not reach statistical significance. The normalized stride width increased significantly in patients with DMD compared with Ctrls (*p*: <0.001). The anteversion of pelvic tilt was increased in participants with DMD compared to Ctrls across the whole gait cycle (*p*: <0.001). The pelvic tilt range of motion did not differ significantly between subjects with DMD and Ctrls (*p*: 0.059) but double bump pattern was evident (see Fig. 1 for the kinematics plot). At initial contact (IC), the pelvis of subjects with DMD showed an increased anteversion (*p*: 0.003) and elevation (*p*: <0.0001). An increase of the pelvic range of motion on frontal plane was observed in the group of patients with DMD (*p*: 0.036). Pelvic rotation showed a wider range of motion in participants with DMD compared to Ctrls (*p*: 0.029). An increased hip abduction (*p*: 0.004) was found in patients with DMD which is coherently with increased stride width. A reduced knee flexion at IC was found in patients with DMD (*p*: 0.003) with a reduced peak of flexion in both stance and swing phases (*p*: <0.0001 and *p*: 0.005 respectively). The knee extension peak in stance phase increased in subjects with DMD group (*p*: 0.006). The ankles were plantarflexed at IC in the group of patients with DMD (*p*: <0.0001). An averaged increased plantar flexion across the whole gait cycle was observed in the group of subjects with DMD (*p*: <0.0001). Specifically, a reduction in ankle dorsiflexion peaks in both stance and swing phases (*p*: <0.0001; *p*: <0.0001, respectively) and an increased plantarflexion peak at toe-off (*p*: <0.001) were observed in boys with DMD. No significant difference in foot progression angles was observed.

Considering the fact that looking for a correlation between the clinical assessment and gait parameters and exploring the differences between patients with DMD and controls are two different aims, we included all 29 gait variables in the correlation analysis (Table 4). The correlation between the NSAA and the 29 selected gait variables showed a significant negative strong correlation with the stride width (*p*: 0.001, Rho: −0.678) and a strong positive correlation with the normalized walking speed (*p*: 0.0016, Rho: 0.671). Data obtained from the NSAA showed a very strong positive correlation with the ankle mean angle, across the whole gait cycle (*p*: <0.0001, Rho: 0.854), and with the peaks of ankle dorsiflexion in both stance and swing phases (*p*: <0.0001, Rho: 0.836; *p*: <0.0001, Rho: 0.858, respectively). Ankle angle at IC and plantarflexion peak showed a strong positive correlation with NSAA scores (*p*: <0.001, Rho: 0.719; *p*: <0.001, Rho: 0.717). Strong positive correlation was found between hip mean angle on frontal plane and 6MWT (*p*: <0.0001, Rho: 0.850). The NSAA showed a strong positive correlation with the 6MWT (*p*: <0.001, Rho: 0.870).

4. Discussion

4.1. Gait analysis

Our results confirm the specific and well-known gait pattern of children with DMD, characterized by significant increase in the range of pelvic tilt and increase in plantar

Table 3
Comparison between selected spatiotemporal and kinematics variables obtained from DMD and Ctrls groups.

Variable name	DMD ($n=19$)			Ctrs ($n=17$)			Difference p-val
	Mean (SD)	Median	Range	Mean (SD)	Median	Range	
Normalized walking speed	0.35 (0.08)	0.37	0.30	0.41 (0.06)	0.41	0.19	0.009*
Normalized stride length	1.34 (0.22)	1.44	0.68	1.45 (0.15)	1.42	0.56	0.104
Stride time#	1.03 (0.14)	0.99	0.62	0.96 (0.10)	0.98	0.33	0.241
Cadence	118.34 (14.49)	121.01	61.92	126.24 (13.90)	122.87	46.08	0.105
Normalized stride width	0.30 (0.06)	0.29	0.21	0.23 (0.03)	0.23	0.11	<0.001*
Double support time	0.21 (0.05)	0.20	0.20	0.18 (0.04)	0.19	0.13	0.059
Pelvis tilt mean angle	17.09 (6.45)	15.68	22.83	11.60 (3.55)	12.31	16.72	0.003*
Pelvis tilt ROM	5.41 (1.80)	5.18	6.81	4.50 (0.85)	4.48	3.53	0.059
Pelvis tilt angle at IC	17.87 (6.78)	16.76	24.85	11.87 (4.13)	12.42	19.47	0.003*
Pelvis obliquity ROM	12.94 (5.47)	12.41	20.85	9.60 (3.31)	8.90	10.83	0.036*
Pelvis obliquity angle at IC	4.04 (2.36)	3.79	8.90	0.95 (1.33)	0.52	4.77	<0.0001**
Pelvic rotation ROM#	19.91 (8.33)	18.29	24.86	14.04 (4.24)	13.45	16.41	0.029*
Hip flex-ext ROM#	43.83 (5.19)	45.28	16.67	46.65 (5.51)	45.94	19.44	0.205
Hip add-abd mean angle	−0.83 (2.83)	0.06	9.81	1.56 (1.56)	1.81	5.69	0.004*
Hip max flex	43.73 (8.74)	43.20	33.26	41.88 (6.26)	42.18	19.52	0.477
Hip maxext	−0.10 (9.88)	−2.07	35.94	−4.77 (4.19)	−4.57	15.43	0.072
Knee flex-ext ROM	60.49 (5.34)	60.32	16.87	61.22 (3.53)	61.63	15.74	0.635
Knee flex at IC	6.40 (5.21)	7.09	19.56	11.94 (5.18)	12.98	17.14	0.003*
Knee max flex in stance#	13.91 (5.37)	14.22	21.29	24.76 (7.81)	23.82	24.51	<0.0001**
Knee max flex in swing	63.12 (4.87)	63.02	22.05	68.48 (5.86)	68.55	20.19	0.005*
Knee max ext in stance	3.15 (5.31)	4.46	20.87	8.26 (5.11)	8.51	20.62	0.006*
Ankle flex-ext mean angle	−4.15 (5.91)	−2.84	20.66	5.22 (4.34)	5.06	17.19	<0.0001**
Ankle flex-ext ROM	29.88 (7.22)	27.47	26.37	29.52 (4.79)	29.69	16.95	0.864
Ankle flex at IC#	−8.28 (6.00)	−7.41	21.04	2.62 (4.23)	2.40	19.07	<0.0001**
Ankle max dorsiflex in stance	6.70 (6.74)	8.76	22.73	16.25 (5.27)	15.58	19.27	<0.0001**
Ankle max dorsiflex in swing	−4.46 (7.28)	−3.36	24.54	7.73 (3.74)	7.41	16.76	<0.0001**
Ankle max plantar flex	−22.47 (9.24)	−21.81	34.00	−11.20 (8.38)	−9.22	27.63	<0.001*
Foot progress rotation mean angle	−7.08 (8.78)	−5.72	29.84	−6.34 (3.51)	−5.90	10.87	0.739
Foot progress rotation ROM	18.90 (6.84)	18.04	21.80	15.94 (3.53)	15.51	11.75	0.109
NSAA#	21.8 (10.0)	23	28	/	/	/	/
6MWT (m)	434.6 (96.4)	470	280	/	/	/	/

Descriptive statistics of all variables enrolled in this study and comparison of spatiotemporal and kinematic variables between DMD group and Control group (Ctrls).

the variable was not normally distributed in at least one of the two groups.

* p-value < 0.05 compared between DMD and Ctrls.

** p-value < 0.0001 compared between DMD and Ctrls. /: no data for the cell.

flexion of the ankle. Comparison between gait patterns of subjects with DMD following different cortisone treatments do not show statistical differences in any of the investigated variables. In line with a previous report [24], this finding suggests that corticosteroid treatment does not significantly affect the gait characteristics of subjects in this population. Moreover, this result confirms that our analysis has not been compromised by the different pharmacological regimens. The data obtained from spatiotemporal parameters agree with previous reports which confirmed that gait velocity showed a tendency to a reduction, with not statistical significance in [24,34] but with statistical significance in our study, when normalized to anthropometric characteristics. In line with D'Angelo et al. [24], we found reduced normalized step length, but in the absence of statistical significance. This discrepancy could be due to the sample size. Further investigation with a bigger sample size could reduce inter-subject's discrepancies thus providing more reliable results. Forefoot strike at IC and the reduction in step length were shown to be correlated. This correlation represents a strategic gait solution allowing vertical energy conservation through the storing and returning of elastic energy when contractile muscle activity is reduced in subjects with elongated tendons and shorter muscle bellies [35–37]. The increase of the width of the support base agreed with previous investigation and it is reported to increase balance and foot clearance when increased plantar flexion is maintained during the gait cycle [24]. The kinematic variables of the pelvis on sagittal plane showed an increased anteversion angle across the whole gait cycle as suggested in previous studies [21,24]. The pelvic range of motion on sagittal plane in our sample did not differ from the Ctrls, in contrast to Doglio et al. [25] who found this variable increased. This discrepancy could be due to the difference in age and homogeneity of the groups of subjects with DMD involved in the two studies. We found an increased pelvic anteversion and elevation angle at IC not previously reported. Increased anteversion of the pelvis could be due to hip muscles weakness or to a hip flexor contracture. To attain stability of the pelvis on the hips, boys with DMD "hang" the pelvis on the hamstrings during the

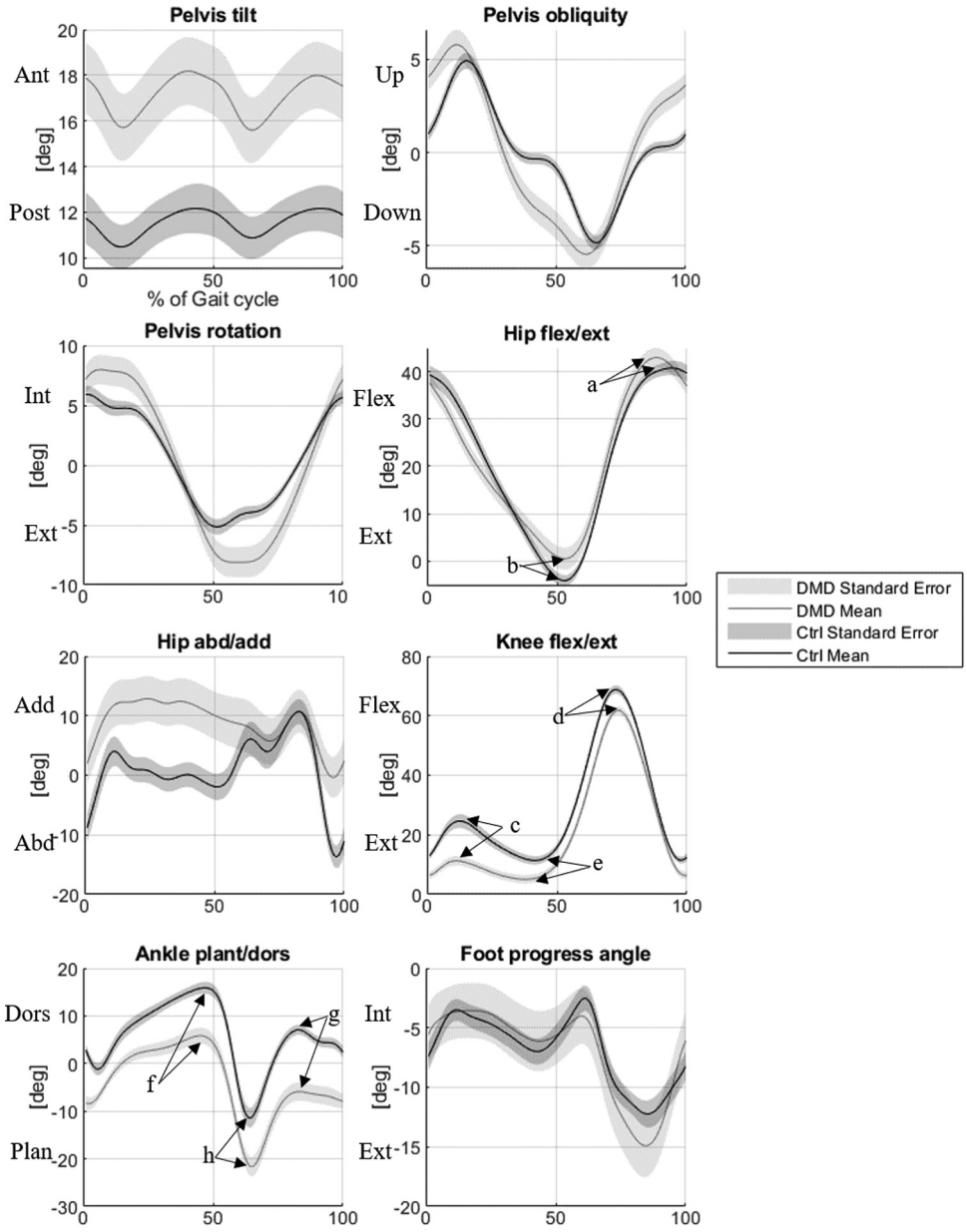

Fig. 1. Graphical representation of main joint movements during whole gait cycle at natural velocity of patients with DMD and Ctrls.
Pelvic movements are collected on sagittal (tilt), frontal (obliquity) and transverse (rotation) planes. Hip movements are referred to sagittal (flex/ext) and frontal (abd/add) planes. Knee and ankle movements are collected on sagittal plane (flex/ext and plant/dors respectively). The foot progress angle represents the inclination of the foot in respect to the direction of walking. The arrows indicate at which point of the curve the following parameters were calculated: a = Hip max flex; b = Hip max ext; c = Knee max flex in stance; d = Knee max flex in swing; e = Knee max ext in stance; f = Ankle max dorsiflex in stance; g = Ankle max dorsiflex in swing; h = Ankle max plantar flex.

support phase, exploiting the lengthening of these muscles to maintain upright posture. This attitude, together with the progression of the disease, could cause the shortening of the hip flexor muscles. Increased pelvic elevation at IC coincident with the one at terminal swing (Fig. 1) may be due to the forefoot strike pattern as it requires increased pelvic elevation or knee flexion (not present in our sample). Increased pelvic rotation range of motion and increased pelvic elevation in terminal swing could be interpreted as a useful strategy to improve step length [25]. At the hip, we observed an increased mean flexion angle across the whole gait cycle that is consistent with increased pelvic anteversion. Consistent with the increased stride width, the more abducted hip mean angle on the frontal plane found in patients with DMD supports the observations reported by Gaudreault et al. [23]. We were not able to replicate previously reported results for increased knee range of motion [24,25]. A reduced knee flexion at IC was found also by D'Angelo et al. [24] but did not reach statistical significance in our investigation. A reduced knee flexion peak and an increased knee extension peak in stance were supported by previous publications. It is known that if the ankle is positioned more in plantar

Table 4
Correlation analysis between North Star Ambulatory Assessment (NSAA), Six Minutes Walking Test (6MWT) and selected spatiotemporal and kinematics variables.

Variable name	NSAA[#]			6MWT		
	p-val	Rho	r-squared	*p*-val	Rho	r-squared
Normalized walking speed	0.0016[*]	0.671[§]	0.537	0.021	0.629[§]	/
Normalized stride length	0.0023	0.654[§]	0.520	0.009	0.691[§]	/
Stride time[#]	0.005	−0.612[§]	0.380	0.174	−0.402	0.285
Cadence	0.005	0.612[§]	0.405	0.071	0.516	/
Normalized stride width	0.001*	−0.678[§]	0.570	0.013	−0.664[§]	/
Double support time	0.028	−0.503	0.339	0.155	−0.418	/
Pelvis tilt mean angle	0.023	−0.518	0.339	0.465	−0.223	/
Pelvis tilt ROM	0.251	−0.277	0.064	0.332	−0.293	/
Pelvis tilt angle at IC	0.029	−0.500	0.318	0.474	−0.218	/
Pelvis obliquity ROM	0.244	−0.281	0.120	0.338	−0.289	/
Pelvis obliquity angle at IC	0.041	−0.473	0.336	0.072	−0.514	/
Pelvic rotation ROM[#]	0.031	−0.496	0.251	0.125	−0.451	0.282
Hip flex-ext ROM[#]	0.270	0.267	0.123	0.949	−0.022	0.027
Hip add-abd mean angle	0.004	0.626[§]	0.491	<0.001*	0.850[§§]	/
Hip max flex	0.032	−0.493	0.346	0.228	−0.359	/
Hip maxext	0.002	−0.662[§]	0.496	0.122	−0.451	/
Knee flex-ext ROM	0.485	0.171	0.044	0.898	0.039	/
Knee flex at IC	0.026	−0.508	0.290	0.092	−0.487	/
Knee max flex in stance[#]	0.132	0.358	0.002	0.325	0.297	0.003
Knee max flex in swing	0.473	−0.175	0.094	0.088	−0.492	/
Knee max ext in stance	0.147	−0.346	0.186	0.160	−0.414	/
Ankle flex-ext mean angle	<0.0001**	0.854[§§]	0.759	0.028	0.605[§]	/
Ankle flex-ext ROM	0.898	−0.032	0.002	0.333	−0.292	/
Ankle flex at IC[#]	<0.001*	0.719[§]	0.650	0.060	0.534	/
Ankle max dorsiflex in stance	<0.0001**	0.836[§§]	0.721	0.037	0.583	/
Ankle max dorsiflex in swing	<0.0001**	0.858[§§]	0.783	0.023	0.622[§]	/
Ankle max plantar flex	<0.001*	0.717[§]	0.415	0.059	0.535	/
Foot progress rotation mean angle	0.112	−0.377	0.132	0.202	−0.378	/
Foot progress rotation ROM	0.522	−0.157	0.021	0.247	−0.346	/
NSAA[#]	/	/	/	<0.001*	0.870[§§]	0.754
6MWT (m)	<0.001*	0.870[§§]	0.754	/	/	/

Output of correlation analysis between North Star Ambulatory Assessment (NSAA), Six Minutes Walking Test (6MWT) and selected spatiotemporal and kinematics variables.
[#] the variable was not normally distributed in the DMD group.
[*] *p*-value < 0.05 for the existence of a relationship between NSAA and selected variable.
[**] *p*-value < 0.0001 for the existence of a relationship between NSAA and selected variable.
[§] strong correlation coefficient (> 0.6 or < −0.6).
[§§] very strong correlation coefficient (> 0.8 or < −0.8). /: no data for the cell.

flexion during stance, the ground reaction force is closer to the knee joint center, reducing internal knee extension torque and accommodating the weak quadriceps [20]. However, this biomechanical configuration can force the knee into hyper-extension during stance phase [24,25]. Conversely, our findings on reduced knee flexion peak in swing phase do not agree with previous investigations that found an increased flexion peak in swing [24,25]. As increased knee flexion could be assumed to be a compensatory strategy to aid foot clearance during swing [20,24,25] this discrepancy could be caused by two different strategies to avoid tripping or falling: one based on pelvic elevation and the other based on increased knee flexion. Reduction in dorsiflexion at IC and during both stance and swing peaks confirm previous reports [5,21,24,25]. We found an increase in the peak of plantarflexion during pre-swing not observed in previous investigations [24,25]. The progressive replacement of the contractile muscle tissue by non-contractile fibrofatty tissue in the gastrocnemius muscle and the above-mentioned elastic energy storage and return strategy, could lead to a reduction in ankle mobility pulling the ankle toward plantar flexion [22, 36,38].

4.2. Correlation between clinical and instrumental assessments

To the best of our knowledge, this is the first study to explore the correlations between 3D gait variables and standard functional measures in populations with DMD. We specifically aimed to establish if gait analysis may provide objective and technology-assisted clinically relevant parameters, reflecting functional disability more precisely than a purely clinical assessment.

Our findings show that the enlargement of the support base, the walking speed and the increased plantar flexion during the whole gait cycle correlated significantly with the

NSAA score. All these parameters are very representative of walking ability. The increase of the step width could be assumed to be an index of reduced stability of the subjects which consequently influences the quality of ambulation and postural changes in children with DMD. From our data, it is evident that there is a good direct correlation between walking speed and NSAA score, as the slower walker had more severe motor impairment. We can speculate that the observed reduction of gait speed in correlation with NSAA could be a clinically relevant parameter, even if in the previous investigation the walking speed of subjects with DMD does not differ from that of typically developed children [24]. Moreover, gait velocity and step length has been reported to be affected by increased plantarflexion at IC [35–37]. At the ankle level, we found a reduction of the dorsiflexion peaks in both stance and swing phase, a wider ankle angle at IC and higher peak of plantar flexion at foot off with significant direct correlation with NSAA. Therefore, in our sample, ankle plantar flexion seems to affect gait velocity and represents the main aspect of gait that determines functional disability as highlighted by NSAA score. All the above-mentioned parameters are easily assessed and could be early markers of the disease. As it is well-known from natural DMD history, ankle contracture is the first musculoskeletal deformity to appear and affects walking ability early [1]. With 3D gait analysis we are able to measure in a dynamic condition the behavior of the ankle in all phases of the gait cycle. Therefore, the assessment of ankle kinematics could be an index of ambulatory abilities from the early stages of the disease. However, further research including larger samples and different age groups will be needed to confirm this hypothesis, as well as longitudinal research designs to better understand the functional implications of the disease progression.

Surprisingly, our data did not show any correlation between gait parameters and 6MWT. The only correlation we found was between averaged hip angle on the frontal plane, but this was not supported by the correlation with stride width and was therefore not taken into account. The absence of correlations between 6MWT and the selected variables supports the concept that the walking endurance could not be influenced by single joint kinematic abnormalities or spatiotemporal variables. Since several adaptive adjustments can compensate for anomalies present in single joint movements, the investigated variables cannot be considered representative of the functional result obtained at 6MWT in the population with DMD. Moreover, as highlighted in several clinical trials, 6MWT has certain limitations, such as the impact of age at baseline or the interference of a growth effect. Finally, in the early stages of the disease, 6MWT fails to detect gait abnormalities, resembling normal motor function [18].

From 3D gait analysis we first identified the stride width and ankle kinematics (specifically with the mean ankle angle during whole gait cycle and with ankle dorsiflexion peak in swing) as the main representative gait parameters of global ambulatory status in children with DMD measured with NSAA. This finding was supported by previous publications [24,25] which speculated about the effects of ankle kinematics on knee and hip kinematics.

The representative gait parameters identified could be selected as useful outcomes in clinical trials. Future investigations should be done to support our findings and to reach consensus on kinematics in this population. Based on our results, we suggest increasing the use of 3D gait analysis in the early stages of the disease to obtain objective and reliable measures with which to follow, in a longitudinal way, the progression of the disease. Obviously, further research should be carried out to obtain longitudinal data and to prove the sensibility to change of the above-mentioned measures.

In a rehabilitative setting, it is crucial to obtain a global and exhaustive evaluation of gait pattern to prevent and reduce abnormal motor behavior which leads to the development of secondary musculoskeletal deformities. We therefore suggest using functional scales like NSAA and endurance scale like 6MWT as a complementary measure to reach a comprehensive assessment of gait.

One limitation of this study was the absence of a systematic evaluation of the passive range of motion of the main joints and of foot deformities such as midfoot break that could affect ankle kinematics on the sagittal plane [20]. Another limitation was the absence of analysis of interlimb joints coordination which could represent an ambitious future deepening in this field. Our group of subjects with DMD has a wide range of disease duration which represents a selection bias. In our sample, only 13 subjects with DMD performed a complete protocol with 6MWT and that could lead to an increase in statistical error. Finally, as DMD is a progressive and rare disease, comparison with other studies was difficult due to the relative homogeneity of the studied samples.

Because ankle movement strongly correlates with clinical ambulatory assessment and affects the kinematics of all the investigated joints as mentioned above, we suggest a further study with cluster sampling based on type of foot strike (i.e. forefoot, flatfoot or heel strike). As proposed in previous investigations, walking speed and length are influenced by the type of foot strike [35,36]. Therefore, the type of the foot strike could be a discriminating factor between two stages of progressive abnormalities of the walking pattern.

In conclusion, in this study we approached 3D gait analysis in DMD from a different point of view, with the specific aim of providing objective and accurate indexes of motor disability, surmounting the limitations of clinically-based assessment tools. Therefore, after performing a comparison of 3D gait analysis between boys with DMD and an age-matched normally developed children's group, we calculated for the first time the correlations between selected gait parameters and standard clinical scores, such as specific functional outcome measures like NSAA and 6MWT.

Our results thus help to understand the kinematic characteristics of this population and to increase our knowledge about a field where consensus is still lacking

[20]. Moreover, interestingly, we identified the gait speed, the support base width and the ankle kinematics presenting a strong correlation with NSAA, which proved particularly useful in characterizing the motor ambulatory function, even at an early stage of the disease. Despite several limitations, our preliminary results may have significant implications in clinical practice. However, confirmatory research studies are needed, especially in a longitudinal perspective, in order to verify: the sensitivity to change, the reliability and the consistency of these measures.

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