Gait strategy in genetically obese patients: A 7-year follow up

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1. Background

Prader–Willi syndrome (PWS) is a rare condition, representing the most common form of genetic obesity. PWS affects multiple body systems and its most consistent characteristics include muscular hypotonia, hyperphagia, leading most subjects to develop morbid obesity from early childhood, dysmorphogenetic abnormalities, behavioral disorders and cognitive impairment, hypogonadism and growth failure (Cassidy, Schwartz, Miller, & Driscoll, 2012). General health status is usually preserved in individuals with PWS. Obesity is a common feature in PWS and it is often massive; many individuals with PWS exceed by more than 200% their ideal body weight. Motor problems are most prominent in infancy, but continue to be of clinical importance in adulthood, due to hypotonia, decreased muscle mass and the excessive amount of fat, which

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influences the biomechanics of activities of daily living, causing and increasing functional limitations over time (Capodaglio et al., 2009; Menegoni et al., 2009; Vismara et al., 2007). Within the wide spectrum of physical and intellectual disabilities associated with PWS, musculoskeletal diseases represent a serious issue, as they affect a significant proportion of individuals with PWS. Therefore, rehabilitation, physical activity interventions and surveillance play a key role in achieving the highest possible quality of life, especially in the light that PWS adults with lower body mass indexes (BMI) show a near-to-normal life expectancy.

Some studies have already focused on the quantification of motor performance in individuals with PWS, evidencing an abnormal gait pattern and postural ability and a delay in performance maturation when compared to normal weight subjects or BMI-matched non-genetically obese subjects (Butler et al., 2002; Capodaglio et al., 2009; Cimolin et al., 2010; Cimolin, Galli, Rigoldi, Grugni, Vismara, & Mainardi, 2011; Cimolin, Galli, Vismara, Grugni, Camerota, & Celletti, 2011; Cimolin, Galli, Vismara, Grugni, Priano, & Capodaglio, 2011; Galli et al., 2011; Kroonen, Herman, Pizzutillo, & MacEwen, 2006; Reusa et al., 2011; Vismara et al., 2007). The functional effects of weight loss after bariatric surgery (Aaboe, Bliddal, Messier, Alkjær, & Henriksen, 2011; Hortobagyi, Herring, Pories, Rider, & DeVita, 2011; Messier, Gutekunst, Davis, & DeVita, 2005; Vartiainen et al., 2012) or after short-term cyclical training (no later than 1 year) in obese subjects (Capodaglio et al., 2011; Reus, van Vlimmeren, Staal, Otten, & Nijhuis-van der Sanden, 2012; Vismara et al., 2010) have been also investigated. However, the effect of weight loss on gait is still controversial (Aaboe et al., 2011; Cimolin et al., 2013; Fontana et al., 2009; Messier et al., 2005; Vartiainen et al., 2012). We should bear in mind that in other genetically obese conditions, like in Down Syndrome, adults show precocious age-related changes in physiologic function and motor performance as compared to their counterparts: a decreased ability to perform activities of daily living and an earlier onset of age-related medical problems, such as osteoarthritis, hearing loss, and dementia, have been demonstrated in Down syndrome (Lott & Head, 2001). We can speculate that also in PWS patients, who share common features like muscular hypotonus, ligament laxity and obesity with Down syndrome, a similar decreased performance capacity may well be present. However, there is a lack of evidence in the literature and no longitudinal studies have been reported in PWS individuals. In particular, in this study we focused the attention on gait, as walking is a fundamental task for everyday life and the most common modality of prescribed physical activity. Eventual gait differences at long-term follow-up in PWS could be important for evaluating the effects of rehabilitative and weight loss programs on function. Therefore, our goal was to describe long term changes in gait biomechanics using 3D-gait analysis as well as in body mass in PWS subjects.

2. Materials and methods

2.1. Participants

Eight adult patients with a diagnosis of PWS were enrolled in this study (Table 1). All patients showed the typical PWS clinical phenotype (Cassidy et al., 2012). Cytogenetic analysis was performed in all participants. Seven patients had interstitial deletion of the proximal long arm of chromosome 15 (del15q11-q13), while uniparental maternal disomy for chromosome 15 (UPD15) was found in the remaining subject. Incomplete development of secondary sex characteristics was present in both genders. In males, testes were palpable with a volume of less than 6 ml. Primary amenorrhea was present in 3 subjects, while the remaining female suffered from irregular menses. Three females were undergoing sex steroid replacement treatment. Two hypertensive patients were on treatment with angiotensin-converting enzyme inhibitor plus Ca-antagonist and loop diuretics, respectively. One of the hypertensive patients had type 2 diabetes and was treated with insulin. No patient was undergoing weight-reducing medical therapy. Four patients were receiving treatments with neuroleptics. Six PWS were treated with growth hormone (GH). Mean duration of GH treatment was 9.7 years (range 8.1–10.1 years).

All PWS subjects showed mild mental retardation. In this respect, one of the requirements for participating in the study was a score over the cut-off value of 24 in the Mini Mental State Examination (MMSE) Italian version (Neri, Andermacher, Spanó, Salvioli, & Cipolli, 1992). Scores over the MMSE cut-off are recognized as suggesting the absence of widespread acquired cognitive disorders in adult people. In this light, our PWS patients were all able to understand and complete testing.

Table 1
Clinical characteristics of the study groups.

	PWS patients		HCG	OCG
	T0	T1		
Participants (M/F)	8 (4/4)		10 (5/5)	14 (5/9)
Age (years)	28.7 ± 4.6	36.4 ± 5.1	33.4 ± 9.6	29.4 ± 7.9
Weight (kg)	$102.7 \pm 21.7^{+}$	$87.2 \pm 24.5^{*,+}$	$66.9 \pm 8.5^{\S}$	101.2 ± 12.9
BMI (Kg/m^2)	$44.2 \pm 6.4^{+}$	$37.4 \pm 5.9^{*,+}$	$22.8 \pm 3.2^{\S}$	40.2 ± 3.3
*All values are mean ± SD				

* $p < 0.05$, PRE versus POST.
\+ $p < 0.05$, if compared to HCG.
§ $p < 0.05$, if compared to OCG.

Two different groups of subjects were specifically recruited for this study and served as controls. The first group included 14 non-genetically obese patients (OCG: obese control group); the second group included 10 age-matched healthy individuals (HCG: healthy control group). Inclusion criteria for the HCG were no cardiovascular, neurological or musculoskeletal disorders. They had normal flexibility and muscle strength and no obvious gait abnormalities. All participants had normal values in the main laboratory tests, including adrenal and thyroid function. On admission, our PWS subjects were able to walk independently without aids.

The study was approved by the Ethics Research Committee of the Istituto Auxologico Italiano. Written informed consent was obtained by patients, where applicable, or their parents.

2.2. Methods

PWS subjects had been assessed in two different occasions: the first assessment at admission to our Rehabilitation Hospital (T0 session) for comprehensive rehabilitation programs and weight management and the second assessment at admission to our hospital 7 years later (T1 session). During the 7 years between the two evaluations, PWS subjects underwent out-patient rehabilitation programs and were occasionally admitted for in-patient rehabilitation. Yearly follow-ups were provided.

Following baseline evaluation, individual dietary prescriptions consisted of 75% of total daily resting energy expenditure (kilocalories per 24 h), estimated by computed open-circuit indirect calorimetry (Sensormedics 29, Anaheim, CA). Physical activity was unchanged during the study.

Physical examination included determination of height and weight under fasting conditions and after voiding. Standing height was determined by a Harpenden Stadiometer and expressed as centimeters. Body weight was measured to the nearest 0.1 kg on a precision digital scale, with the subject dressed in shorts and T-shirt. BMI was defined as weight/height^2 (kg/m^2).

For gait pattern characterization, all participants, both PWS and obese and healthy subjects, were evaluated using video recording and 3D GA. GA was performed using an optoelectronic system with 6 cameras (460 VICON, Oxford Metrics Ltd., Oxford, UK) with a sampling rate of 100 Hz, and two force platforms (Kistler, CH). To evaluate the kinematics of each body segment, passive markers were positioned on each participant's body, as described by Davis, Ounpuu, Tyburski, and Gage (1991). After placement of the markers, individuals were asked to walk barefoot at their own natural pace (self-selected speed) along a walkway containing the force platforms at the mid-point. Five acquisitions comprehensive of kinematic and kinetic data were collected for each patient in order to guarantee data reproducibility.

2.3. Data analysis

All graphs obtained from GA were normalized as a percentage of gait cycle and kinetic data were normalized for individual body weight. For each participant (both patients and healthy controls) starting from the five trials collected, three consistent trials able to evidence the same gait pattern (spatio-temporal, kinematic and kinetic) were extracted and considered for the analysis. From these data we identified and calculated the parameters described in Table 2. This procedure was conducted by the same operator to assure reproducibility of data analysis.

2.4. Statistical analysis

All the previously defined parameters were computed for each participant and then the mean values and standard deviations of all indexes were calculated for each group.

The Kolmogorov–Smirnov test was used to verify whether the parameters were normally distributed. However, the parameters were not normally distributed, so we used the Wilcoxon paired test between the T0 and T1 sessions in order to determine whether the weight alteration introduced statistically significant changes. The patients' and the controls' data were compared with Kruskal–Wallis test followed by post hoc comparison. Null hypotheses were rejected when probabilities were below 0.05.

Further the differences between proximal and distal subgroups were estimated using the Cohen effect size (d') (Cohen, 1988). Responsiveness is considered to be "trivial" for $d' < 0.20$, "small" for $0.20 < d' < 0.50$, "moderate" for $0.50 < d' < 0.80$, and "large" for $d' > 0.80$.

3. Results

At the end of the study, BMI was significantly reduced in PWS group, obesity by a type III to an obesity type II (Table 1). In Table 3, we reported the mean values and standard deviations of the spatio-temporal, kinematic and kinetic parameters considered in this study for PWS (at T0 and T1), OCG and HCG.

At T0 session, most of the spatio-temporal parameters were significantly different between individuals with PWS, OCG and HCG. Patients walked with a reduced cadence, a shorter normalized step length and at a slower velocity, compared to the two control groups. The pelvis was characterized by greater ROM on the sagittal plane (PT-ROM index) and high flexed hip position during the entire gait cycle (HIC and HmSt indices with a reduced ROM if compared to HCG. Knee joint was flexed at

Table 2
Gait parameters and descriptors.

Gait parameter	Description
Spatio-temporal parameters	
% stance (%gait cycle)	% of gait cycle that begins with initial contact and ends at toe-off of the same limb;
Step length	Longitudinal distance from one foot strike to the next one, normalized to subject's height
Cadence (step/min)	Number of step for
Velocity (m/s)	Mean velocity of progression
Kinematics (*degrees*)	
PT-ROM	The range of motion at pelvis on the sagittal plane (pelvic tilt graph) during the gait cycle, calculated as the difference between the maximum and minimum values of the plot;
HIC	Value of hip flexion–extension angle (hip position on the sagittal plane) at initial contact, representing the position of hip joint at the beginning of gait cycle
HmSt	Minimum of hip flexion (hip position on sagittal plane) in stance phase, representing the extension ability of hip during this phase of gait cycle
H-ROM	The range of motion at hip joint on the sagittal plane (hip flex-extension graph) during the gait cycle, calculated as the difference between the maximum and minimum values of the plot;
KIC	Value of knee flexion–extension angle (knee position on sagittal plane) at initial contact, representing the position of knee joint at the beginning of gait cycle
KmSt	Minimum of knee flexion (knee position on sagittal plane) in mid-stance, representing the extension ability of knee during this phase of gait cycle
KMSw	Peak of knee flexion (knee position on sagittal plane) in swing phase, representing the flexion ability of knee joint during this phase of gait cycle
K-ROM	The range of motion at knee joint on the sagittal plane (knee flex-extension graph) during the gait cycle, calculated as the difference between the maximum (KMSw) and minimum (KmSt) values of the plot;
AIC	Value of the ankle joint angle (on sagittal plane) at the initial contact, representing the position of knee joint at the beginning of gait cycle
AMSt	Peak of ankle dorsiflexion (on sagittal plane) during stance phase, representing the dorsiflexion ability of ankle joint during this phase of gait cycle
AmSt	Minimum value of the ankle joint angle (on sagittal plane) in stance phase, representing the plantarflexion ability of ankle joint at toe-off
AMSw	Peak of ankle dorsiflexion (on sagittal plane) during swing phase, representing the dorsiflexion ability of ankle joint in this phase of gait cycle
A-ROM	The range of motion at ankle joint on the sagittal plane (ankle dorsi-plantarflexion graph) during the stance phase of the gait cycle, calculated as the difference between the maximum (AMSt) and minimum (AmSt) values of the plot;
Kinetics	
AMMax (N*m/Kg)	The maximum value of ankle plantarflexion moment during terminal stance
APMax (W/Kg)	The maximum value of generated ankle power during terminal stance (maximum value of positive ankle power during terminal stance), representing the push-off ability of the foot during walking
APMax norm (W*s/Kg*m)	The maximum value of generated ankle power during terminal stance (maximum value of positive ankle power during terminal stance) normalized to the velocity of progression

initial contact (KIC index), quite normal in midstance (KmSt index) and swing phase (KMSw and K-ROM indices). Analysis of ankle kinematics displayed a quite normal position during the entire gait cycle, with the exception of reduced plantarflexion ability during terminal stance phase (AmSt index) and ROM (A-ROM index). As for ankle kinetics, the peaks of ankle plantarflexion moment (AMMax index) and of power (APMax index) were limited, representing significantly lower push-off ability than OCG and HCG.

At T1 session significant spatio-temporal changes were observed in terms of velocity, step length and cadence. With regard to the hip joint, there were significant T0–T1 changes in terms of hip position (HIC, HmSt indices) which is less flexed (Fig. 1). Knee flexion–extension showed a reduction of flexion in swing phase (KMSw index) and of its excursion (K-ROM index). No changes of the ankle position were evident. As for ankle kinetics, we observed in POST session higher values for the peak of ankle power in terminal stance (APMax index) in comparison to T0 session. No changes were found in terms of maximum of ankle moment (AMMax index). The APMax index normalized to the velocity of progression (APMax norm index) did not reveal significant differences at T1. All the significant results were confirmed using the exact probabilities for small samples. Moreover, all the significant parameters in the T0–T1 comparison in both groups presented a large effect (Cohen $d' > 0.80$).

4. Discussion

The main goal of this study was to investigate possible biomechanical changes during gait in adult PWS patients at long-term follow-up (7 years). During this lapse of time, PWS subjects underwent in- and out-patient rehabilitation programs including nutritional, physiotherapy and adapted physical activity interventions.

We know that gait in PWS is impaired and it can be described as cautious, and balance capacity is reduced, thus leading to higher risk of fall and fractures (Butler et al., 2002; Kroonen et al., 2006) with related burden in health costs. The novelty of our study is to quantitatively evaluate the change in gait in the long term in PWS subjects using 3D-gait analysis. Our results

Table 3
Spatial–temporal and kinematic parameters of PWS at T0 and T1 session. Data are expressed as mean (standard deviation).

	T0	T1	HCG	OCG	d'
Spatio-temporal parameters					
%stance (% gait cycle)	60.74 (1.64)	62.05 (2.38)	59.57 (1.47)	62.22 (1.28)	0.19
Step length	0.48 (0.04)$^{+,\S}$	0.56 (0.04)$^{*,+,\S}$	0.80 (0.04)	0.76 (0.05)	2.03
Cadence (step/min)	105.40 (4.62)$^{+,\S}$	111.52 (9.31)*	116.80 (4.80)	115.57 (4.60)	0.88
Velocity (m/s)	0.88 (0.09)$^{+,\S}$	1.04 (0.11)*	1.2 (0.17)	1.03 (0.07)	1.54
Kinematics (*degrees*)					
PT-ROM	7.12 (2.93)$^{+}$	6.09 (2.40)$^{+}$	1.61 (3.67)	5.67 (3.46)$^{+}$	0.39
HIC	49.24 (15.94)$^{+}$	38.59 (9.93)*	27.22 (7.54)	43.50 (11.23)$^{+}$	1.13
HmSt	8.64 (10.78)$^{+}$	−4.96 (6.38)*	−11.92 (7.68)	−3.46 (10.71)$^{+}$	2.17
H-ROM	39.25 (6.86)$^{+}$	40.18 (5.90)$^{+}$	45.92 (5.36)	43.45 (4.10)	0.74
KIC	10.99 (6.29)$^{+,\S}$	9.51 (4.53)$^{+,\S}$	4.06 (6.63)	4.93 (7.25)	0.27
KmSt	−0.49 (4.19)	−2.67 (2.93)	0.12 (3.82)	−2.2 (5.94)	0.61
KMSw	55.84 (7.04)	47.09 (7.42)$^{*,+,\S}$	59.01 (6.18)	54.84 (7.34)	1.21
K-ROM	56.75 (6.33)	51.60 (6.33)$^{*,+,\S}$	60.28 (6.31)	58.23 (4.42)	0.82
AIC	−1.61 (9.89)	−1.12 (6.85)	1.81 (4.87)	−1.45 (7.26)	0.06
AMSt	13.59 (6.77)	13.89 (5.15)	12.91 (5.97)	13.95 (3.34)	0.04
AmSt	−7.18 (11.83)$^{+,\S}$	−7.26 (7.78)$^{+,\S}$	−18.98 (6.19)	−15.85 (6.61)	0.01
A-ROM	20.78 (5.04)$^{+,\S}$	21.14 (4.27)$^{+,\S}$	27.72 (6.56)	29.81 (6.88)	0.08
AMSw	11.53 (9.61)	6.77 (6.16)	8.63 (9.93)	5.08 (2.36)	0.06
Kinetics					
AMMax (N*m/Kg)	1.02 (0.17)$^{+,\S}$	0.91 (0.41)$^{+,\S}$	1.68 (0.25)	1.47 (0.13)	0.35
APMax (W/Kg)	1.59 (0.51)$^{+,\S}$	2.03 (0.55)$^{*,+,\S}$	3.73 (0.71)	3.01 (0.52)	0.83
APMax norm (W*s/Kg*m)	1.82 (0.55)$^{+,\S}$	1.95 (0.62)$^{+,\S}$	3.10 (1.06)	2.95 (0.80)	0.23

* $p < 0.05$, T0 versus T1.
$^{+}$ $p < 0.05$, if compared to HCG.
§ $p < 0.05$, if compared to OCG. Cohen effect Size d' is calculated to estimate the difference between T0 and T1 session.

demonstrated that PWS patients show relevant changes in the biomechanical parameters of gait after 7 years. Improvements were present especially in terms of spatial–temporal parameters (velocity, step length and cadence) and at proximal level (hip joint). A significant reduction of the marked hip forward tilt, which is a peculiarity of patients with PWS (Capodaglio et al., 2009; Cimolin et al., 2010, 2011a), was observed at T1. This change at hip level resulted in a shift of the gait pattern closer to the reference one.

In terms of ankle kinetics, PWS patients show lower peak ankle power than CG, meaning a lower propulsion capacity during terminal stance. This result was consistent with previous studies on gait pattern in PWS (Capodaglio et al., 2009; Cimolin et al., 2010, 2011b; Vismara et al., 2007). Two possible hypotheses can be formulated for this limitation. Firstly, lower gait velocity in PWS may affect ankle power. After normalizing APMax index by gait velocity (APMax norm index) no significant differences with controls were evident. Secondly, the reduced push-off may be linked to muscle weakness which is a general feature of these patients. In particular, the triceps surae, mostly responsible for the generation of ankle power, may ineffectively contract during terminal stance (Capodaglio et al., 2009).

The changes in spatial–temporal parameters show important improvements in velocity, step length and cadence. Improving those parameters may ultimately improve well-being and quality of life, increase physical activity and energy

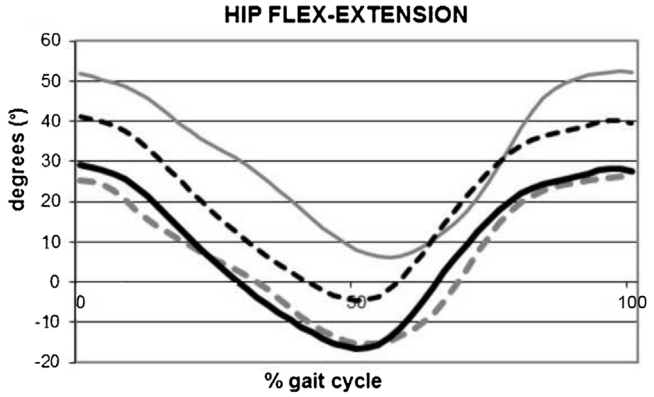

Fig. 1. Hip flex-extension plot of a patient representative of PWS group is represented at T0 (solid gray line) and at T1 session (dotted gray line). The mean value of plot for HCG (solid black line) and OCG (dotted black line) are represented for comparison.

expenditure and reduce the related disability. This was achieved without a substantial modification in the kinetics and kinematics, which might need tailored and specific rehabilitation programs.

Our results evidenced that PWS patients showed positive changes in biomechanical parameters of gait after a 7-year period, during which in- and out-patient rehabilitation programs including nutritional and adapted physical activity interventions were attended by the subjects. In our opinion, the prominent factor in achieving the present results consisted in the significant weight loss at T1 (on average, 15 kg). The latter plays in general an important in improving health status, preventing related diseases and improving activity and participation, according to the International Classification of Functioning psycho-bio-social model. Our data back the recommendation that early interventions on weight management in PWS children represent the gold standard approach to minimize disability. Whether biomechanical changes in gait strategy may occur in early weight loss or if prevention is implemented during childhood, thus allowing the development of motor patterns under normal body weight conditions, remains an interesting uncovered topic.

The main limitation of this study is the small number of participants resulting in limited strength of the statistical findings; however, we have to bear in mind that PWS is a rare genetic condition and large experimental samples are difficult to gather and to follow up in the long term.

Competing interest

All authors have not any conflicts of interest and any financial interest. All authors attest and affirm that the material within has not been and will not be submitted for publication elsewhere.

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