Are there common walking gait characteristics in patients diagnosed with late-onset Pompe disease?

Abstract

Late-onset Pompe disease (LOPD) is a rare disease, defined as a progressive accumulation of lysosomal glycogen resulting in muscle weakness and respiratory problems. Anecdotally, individuals often have difficulties walking, yet, there is no three-dimensional data supporting these claims. We aimed to assess walking patterns in individuals with LOPD and compare with healthy individuals. Kinematic, kinetic and spatiotemporal data were compared during walking at a self-selected speed between individuals with LOPD (n=12) and healthy controls (n=12). Gait profile scores and movement analysis profiles were also determined to indicate gait quality. In comparison with healthy individuals, the LOPD group demonstrated greater thoracic sway (96%), hip adduction angles (56%) and pelvic range of motion (77%) and reduced hip extensor moments (36%). Greater group variance for the LOPD group were also observed. Individuals with LOPD had a slower (15%) walking speed and reduced cadence (7%). Gait profile scores were 37% greater in the LOPD group compared to the healthy group. Proximal muscular weakness associated with LOPD disease is likely to have resulted in a myopathic gait pattern, slower selected walking speeds and deviations in gait patterns. Although individuals with LOPD presented with some common characteristics, greater variability in gait patterns is likely to be a result of wide variability in phenotype spectrum observed with LOPD. This is the first study to examine walking in individuals with LOPD using instrumented gait analysis and provides an understanding of LOPD on walking function which can help orientate physiotherapy treatment for individuals with LOPD.

Keywords: Late-onset Pompe disease, gait profile score, gait abnormalities, three-dimensional gait

1. Introduction

Pompe disease is defined as an autosomal recessive lysosomal storage disorder caused by acid α-glucosidase deficiency (Chan et al., 2016; van der Ploeg & Reuser, 2008). A deficiency of acid α-glucosidase can lead to an accumulation of lysosomal glycogen in multiple tissues, with cardiac, skeletal and smooth muscle cells most affected (Chan et al., 2016; Kishnani & Howell, 2004; van der Ploeg & Reuser, 2008). The progressive accumulation of lysosomal glycogen leads to cellular damage resulting in muscle weakness (Case & Kishnani, 2006; van der Ploeg & Reuser, 2008).

Pompe disease is a rare disease with varied incidences reported, depending on the ethnic group or geographic area examined. Incidences range from 1 in 14000 to 1 in 146000 (Kishnani & Howell, 2004; van der Ploeg & Reuser, 2008). Symptoms associated with Pompe disease can present at any age. The manifestation of the disease in infancy often leads to cardiac and respiratory failure resulting in death within the first year of life (van der Ploeg & Reuser, 2008). Individuals who present with symptoms after the first year have a slower progression of disease and are termed late-onset Pompe disease (LOPD; Case & Kishnani, 2006; van der Ploeg & Reuser, 2008). In 2010, the Pompe Registry, a global observational database of anonymous longitudinal data on patients with Pompe disease, reported 72 patients with LOPD in the UK from a total of 860 adults and children enrolled in the Registry from 29 countries (Roberts, Jones, Millar, & Prasad, 2011). Whilst currently, 200 individuals are estimated to be diagnosed with LOPD in the UK (“Pompe Disease (GSD2),” 2019), only six adult metabolic services are available in the UK. Approximately 39 – 47% of individuals with LOPD use walking aids (Favejee et al., 2018; Van Der Beek et al., 2012) therefore the remaining individuals who walk independently are likely to be significantly lower than the 200 estimated individuals.

Individuals diagnosed with LOPD present with a range of clinical features, which are progressive and predominantly related to skeletal muscle dysfunction (Chan et al., 2016; van der Ploeg & Reuser, 2008). Diagnosing individuals with LOPD is often difficult and delayed owing to similar clinical features to other neuromuscular diseases and variability in the phenotype spectrum and therefore age at diagnosis does not always reflect the onset of symptoms (Chan et al., 2016; Müller-Felber et al., 2007). Symptoms of LOPD include progressive muscle weakness, with proximal muscles weaker then distal, respiratory problems and exercise intolerance (Case & Kishnani, 2006; Chan et al., 2016; van der Ploeg & Reuser, 2008).

A gradual increase in difficulty with tasks such as walking, running and moving against gravity (e.g. climbing, rising from the floor, chair transfers and lifting the arms overhead) is associated with those with LOPD (Case & Kishnani, 2006; Hagemans et al., 2005). Progressive weakness and reduced respiratory function limit the distance an individual can walk and their ability to perform daily activities (Case & Kishnani, 2006; Favejee et al., 2018; Wokke et al., 2008). As the disease progresses individuals become more reliant on medical devices such as walking aids and ventilatory support devices (Hagemans et al., 2005; van der Ploeg & Reuser, 2008; Wokke et al., 2008). Those able to walk without support are often reported as presenting with a myopathic or 'waddling' gait to compensate for the progressive muscle weakness imbalance (Case & Kishnani, 2006; Chan et al., 2016; Hagemans et al., 2005). A myopathic or waddling gait is described as a walking pattern with excessive motion at the hip, pelvis and trunk in the frontal plane as a result of weakness of the proximal leg and hip girdle muscles (Larner, 2016; Van Iersel & Mulley, 2004). Further compensatory movement patterns such as posterior trunk lean accompanied with changes to the lumbar lordosis and anterior or posterior tilt of the pelvis have also been reported (Chan et al., 2016).

Despite such gait abnormalities being assumed to be characteristic of people diagnosed with LOPD, there is limited evidence of this from formal three-dimensional gait analysis studies. McIntosh et al. (2015) compared spatiotemporal characteristics of LOPD individuals with a normative dataset using an instrumented mat (GAITrite®) finding that individuals with LOPD walked with slower speed as a consequence of both shorter steps and lower cadence. Increased step widths were also reported and suggested to be a result of muscular weakness leading to an increased base of support to improve stability. Spatiotemporal characteristics of walking gait can provide substantial information concerning an individual's quality of gait and are often used to assess response to treatment or understand the functional ability of a disease. Yet, further insights to clinical features and gait quality can be assessed using three-dimensional analysis. Gait analysis has been used to evaluate abnormalities in walking in individuals with different pathologies or to evaluate the effect of interventions on individuals (Galey, Lerner, Bulea, Zimbler, & Damiano, 2017). To our knowledge, there is no evidence examining walking gait in individuals with LOPD using three-dimensional gait analysis procedures. Quantifying walking gait patterns using instrumented analysis approaches will help better understand whether all individuals with LOPD walk with a similar gait pattern, or whether individuals function differently, enabling goal setting and individualised treatment approaches to be designed and evaluated.

Although assessing walking gait provides valuable evaluation for both clinical and research purposes, kinematic and kinetic data produced from such analysis is often large and complex and therefore difficult to interpret. Indices have been developed to provide a summary of the analysis. The Gait Profile Score (GPS; Baker et al., 2009) has been used to assess the quality of gait in individuals in a range of patients (Cimolin & Galli, 2014; Schweizer, Romkes, Coslovsky, & Brunner, 2014) with disorders such as cerebral palsy (Baker et al., 2009; Holmes, Mudge, Wojciechowski, Axt, & Burns, 2018; Tsang et al., 2016), stroke (Devetak et al., 2016), Parkinson's disease (Corona et al., 2016) and multiple sclerosis (Morel et al., 2017). GPS has demonstrated good validity with other measures of gait quality such as the Gillette Gait Index (GDI) (Baker et al., 2009) and allows the decomposition of the GPS into a movement analysis profile to give an indication of which joint angle measures contribute to an elevation in GPS (Baker et al., 2009).

This study aims to compare walking gait parameters of LOPD individuals with healthy individuals to identify whether there are common gait characteristics with LOPD. GPS and MAP will be assessed to determine walking gait quality in LOPD individuals. Based on current evidence this study aims to examine several hypotheses: H_1) individuals with LOPD patients will present with signs of a myopathic gait which include increased contralateral pelvic drop, hip adduction and thoracic sway when compared to healthy individuals, H_2) individuals with LOPD will demonstrate greater posterior thoracic lean and either posterior or anterior pelvic tilt during walking compared to healthy individuals, H_3) individuals with LOPD will demonstrate reduced proximal control indicated by reduced hip moments and powers compared to healthy individuals, H_4) GPS and MAPS will be greater in individuals with LOPD compared to healthy individuals and, H_5) individuals with LOPD will demonstrate reduced walking speed, step length, and cadence and greater step width compared to healthy individuals.

2. Methods

2.1 Participants

The Regional Ethical Committee approved the study (IRAS project ID: 121829) and informed consent was obtained from each participant before testing. Patients with LOPD were recruited from the Metabolic Unit at the Salford Royal NHS Foundation Trust. They were recruited for the study if they met the following criteria; 1) aged between 16 and 70 years, 2) had a positive diagnosis of LOPD and 3) were able to walk 50 m or more continuously without the use of a walking aid. The distance achieved during the LOPD

patient's last six-minute walk test (6MWT; measured during hospital clinic appointment within the previous 6 months) was recorded and individuals who were able to walk further than 550 m were excluded from the study as they were considered not to be exhibiting significant walking difficulties. Percentage of predicted 6MWTdistance were calculated (Enright & Sherrill, 1999). Participants for the healthy group were recruited from staff and students at the University of Salford. Exclusion criteria for both groups were; current or previous unresolved pain or neuromusculoskeletal pathology of the trunk, pelvis or lower limb separate to LOPD; severe skin conditions in the areas of marker placement and a body mass index greater than 30.

2.2 Data collection

Data collection followed the same protocol for patients with LOPD and the healthy group. Synchronised kinematic data (100 Hz) and kinetic data (1000 Hz) were collected using 15 cameras (Qualisys Oqus, Gothenburg, Sweden) and four embedded AMTI force plates (Advanced Mechanical Technology, Inc, Newton, MA). Following the CAST marker set technique (Cappozzo, Catani, Della Croce, & Leardini, 1995), passive retro-reflective markers were placed bilaterally on the lower limb at the anterior superior iliac spine, posterior superior iliac spine, lateral and medial femoral epicondyles, lateral and medial malleolli, 1st and 5th metatarsal heads, the base of the 2nd metatarsal and the most posterior aspect of the calcaneus (Jones et al., 2013). Rigid clusters of four non-orthogonal markers were attached to the lateral aspect of the shanks and thighs to track movement (Jones et al., 2013). Three additional markers were placed on the suprasternal notch and the spinous processes of the 2nd and 10th thoracic vertebrae to assess thoracic movement (Armand, Sangeux, & Baker, 2014).

A static trial was collected before the walking trials. Following the opportunity to practice walking in the lab participants completed five barefoot walking trials (10 m) at self-selected speed. Data quality was checked before the removal of markers and trials with marker loss were excluded and further trials collected. LOPD patients are prone to fatigue and respiratory issues (Chan et al., 2016; van der Ploeg & Reuser, 2008), therefore to minimise the effect of fatigue and breathlessness, rate of perceived exhaustion (RPE) was monitored following each walking trial. Adequate rest periods were encouraged and individuals who demonstrated a rise in their RPE above their baseline values were asked to rest until their RPE had returned to baseline values.

2.3 Data analysis

Visual 3D (C-Motion, Inc., Germantown, MD, USA) was used to calculate spatiotemporal values and kinematic and kinetic curves normalised to the gait cycle. Motion and force data were filtered using a Butterworth 4th order bi-directional low-pass filter with cut-off frequencies of 6 Hz and 25 Hz respectively. Joint kinematics for the thorax, hip, knee and ankle were calculated using XYZ Euler rotation sequence equivalent to the joint coordinate system (Grood & Suntay, 1983; Jones et al., 2013), whilst the pelvis was calculated with ZYX Euler rotation sequence (Baker, 2001). The mid-point between the lateral and medial femoral epicondyles and malleoli were used to determine knee and ankle joint centres respectively. Hip joint centres were estimated based on anterior and posterior superior iliac spine marker positions (Bell, Brand, & Pedersen, 1989). Joint kinetic data were calculated using three-dimensional inverse dynamics, and the internal joint moment data were normalised to body weight and height (Nm/(body weight x height)%) (Pinzone, Schwartz, & Baker, 2016). Inertial and geometric segment properties were estimated for each participant (Dempster, 1955; Hanavan, 1964). The mean walking data of the five trials for each participant was calculated.

Discrete outcome measures were obtained from the kinematic and kinetic data. These included maximum thoracic lean and pelvic tilt, thoracic sway (range of movement frontal plane), contralateral pelvic drop, maximum hip adduction angles during stance and maximum sagittal and frontal hip, knee and ankle angles during stance. Maximum hip, knee and ankle moments and powers were also assessed. Quality of each individuals gait was assessed using the Movement Analysis Profile (MAP) and Gait Profile Score (GPS; Baker et al., 2009), which was based on 9 clinically important kinematic variables. Gait quality for each individual was assessed against the healthy group.

Shapiro-Wilks test for normality revealed the spatiotemporal, GPS and MAP were non-parametric; therefore, Mann Whitney U t-tests (SPSS v24) were conducted to compare the differences between the groups. Kinematic and kinetic data are influenced by walking speed (Holden, Chou, & Stanhope, 1997; Samson et al., 2001; Schwartz, Rozumalski, & Trost, 2008; Swinnen et al., 2013). Individuals with LOPD often walk at a slower speed compared to healthy individuals (McIntosh et al., 2015). To adjust for walking speed, we conducted weighted least squared linear regression models with group and walking speed as independent variables. No participants withdrew from this study.

3. Results

Walking gait was assessed in 12 LOPD patients (6 males and 6 females, age 44.42 ± 13.96 years, height 1.76 ± 0.11 m and mass 73.77 ±15.24 kg) and 12 healthy individuals (6 males and 6 females, age 36.38 ± 9.83 years, height 1.72 ± 0.08 m and mass 70.11 ± 13.84 kg). Groups did not differ in age, height nor mass. LOPD patients covered an average distance of 438.6 ± 77.3 m in their last clinical 6MWT, ranging from 283 – 549 m. This equated to 68.7 ± 14.1% (range 52.5 – 96.8%) of predicted distance. Patient characteristics are presented in Table 1.

Table 1 near here

Kinematic and kinetic curves for both groups are presented in the Figure 1 & 2. Kinematic data (Table 2) demonstrated individuals with LOPD had significantly greater thoracic sway (2.86°, P=.001). No differences for maximum thoracic lean (P=.139) or maximum pelvic tilt were apparent (P=.989). However, the LOPD group demonstrated significantly greater (2.39°, P<.002) range of sagittal pelvic motion compared to the healthy group. No differences were observed for contralateral pelvic drop between the groups (P=.114). No differences in maximum hip flexion angles were reported (P=.523), however, the LOPD group presented with significantly greater maximum hip adduction angles (4.16°, P=.043) compared to the healthy group. Knee and ankle movements were similar between the groups (P>.05).

Figure 1 & 2 near here

Table 2 near here

Hip extensor moments were significantly lower (-1.22 Nm/(BW*Ht)%, p=.001) in the LOPD group compared to the healthy group (Table 3). No differences in hip abductor moments were observed (P=.814). Maximum hip absorption powers were not significantly different between groups (P=.592). However, maximum hip generation powers were significantly lower (-1.46 W/(BW*Ht)%, P=.046) in the LOPD group compared to the health group. Knee extensor moments were significantly lower (0.53 Nm/(BW*Ht)%, P=.031) in the LOPD group compared to the healthy group. Whilst knee abductor moments were not significantly different between groups (P>.05). Maximum knee absorption and generation powers were not significantly different (P>.05) between groups. Maximum ankle moments and powers were not significantly different between groups (P>.05). No differences were observed in first and second peak vertical force (P>.05).

Spatiotemporal data, presented in Table 4, demonstrated LOPD individuals had 15% slower average walking speed than controls (P=.039) arising primarily from a 7% lower cadence (P=.008). No differences in stride length were observed. Individuals with LOPD presented with a 27% narrower step width (P=.048) than the control group. Other spatiotemporal data were similar between the two groups.

Table 4 near here

Overall GPS (Figure 3) was significantly greater in individuals with LOPD (7.92 ± 2.00˚) compared to the healthy group (4.98 ± 1.03˚). No differences between left and right GPS and MAPS were observed and therefore only the left side data is presented. The MAP demonstrated significantly greater values for the LOPD group for pelvic obliquity, hip abduction, hip rotation, knee flexion, ankle plantar flexion and foot progression compared to the healthy group.

Figure 3 near here

4. Discussion

Individuals with late-onset Pompe disease presented with some common gait deviations and greater group variability with their walking gait when compared to healthy controls. Our findings partially support our hypotheses where individuals with LOPD demonstrated some evidence of a myopathic gait, lower hip moments, reduced walking speed and cadence, and greater GPS and MAPS indicating reduced gait quality. Whilst, evidence to support common sagittal thoracic and pelvic motions, as previously thought, were not apparent. Although there were some common gait characteristics, the greater variance reported for some kinematic and kinetic outcomes suggests individuals with LOPD present with different gait abnormalities which reflect the high variability in the phenotype spectrum across individuals with LOPD (Chan et al., 2016; Müller-Felber et al., 2007; Schüller, Wenninger, Strigl-Pill, & Schoser, 2012).

Greater thoracic sway and hip adduction angles in the LOPD group compared to the healthy group suggests that individuals with LOPD walked with a myopathic gait, as previously described (Case & Kishnani, 2006; Chan et al., 2016; Schüller et al., 2012). This study is the first study to quantify walking gait in individuals with LOPD and present quantitative evidence supporting a myopathic gait in these individuals. Atrophy and fat infiltration of trunk, pelvic girdle and proximal lower extremity muscles and associated proximal muscular weakness are commonly observed in individuals with LOPD (Alejaldre et al., 2012; Chan et al., 2016; Pichiecchio et al., 2004; Schüller et al., 2012;

Van Der Beek et al., 2012; Wokke et al., 2008). Magnetic resonance imaging (MRI) studies have reported muscle atrophy in the posterior spinal muscles (latissimus dorsi/ multifidus/ longissimus/ quadratus lumborum), abdominal muscles (rectus abdominus/ internal oblique/ external oblique/ transversus abdominus) psoas, hip adductors, rectus femoris, vasti and hamstrings with the progression of disease (Alejaldre et al., 2012; Figueroa-Bonaparte et al., 2016; Pichiecchio et al., 2004). Figueroa-Bonaparte et al. (2016) used handheld myometry to measure lower limb muscle strength, identifying significant weakness (Medical Research Council Scale 1-3) in the trunk flexors/ extensors, hip extensors/ flexors/ adductors and knee flexors in a high proportion of participants. The authors also concluded that these finding correlated with the corresponding muscle MRI scans. Hip abductor weakness (Favejee et al., 2018) and hip flexor weakness (Van Den Berg et al., 2015) has also been reported. Such muscle atrophy is likely to reduce an individual's ability to stabilise the pelvis and trunk, resulting in a 'waddling' or myopathic gait.

Reduced proximal control, indicated by reduced hip moments, in the LOPD group compared to the healthy group is likely to lead to the myopathic gait observed. Greater thoracic sway is likely to be a result of abnormal pelvic and hip motions (Tamaya et al., 2020) and used as a strategy to increase walking speed in individuals with LOPD (Lee, Verghese, Holtzer, Mahoney, & Oh-Park, 2014). The myopathic gait observed in the LOPD group in our study is likely to be compensatory for the proximal muscular weakness associated with LOPD. The observed compensatory movements associated with a myopathic gait are likely to reduce walking efficiency and contribute to fatigue associated with LOPD (Chan et al., 2016; Hagemans et al., 2005).

Anterior or posterior pelvic tilt is another common characteristic of LOPD walking patterns previously suggested (Chan et al., 2016). Individuals in this study did not tend to either anteriorly or posteriorly fix their pelvis. Instead, individuals with LOPD in the current study demonstrated a greater pelvic range of motion in the sagittal plane. Based on previous research (Alejaldre et al., 2012; Chan et al., 2016; Figueroa-Bonaparte et al., 2016; Pichiecchio et al., 2004; Schüller et al., 2012) this could be attributed to severity of atrophy in the trunk and hip muscles which is likely to lead to reduced pelvic control and therefore greater pelvic motion throughout the gait cycle. Excessive pelvic motion, associated with lumbar spine motion (Crosbie, Vachalathiti, & Smith, 1997), in addition to the reduced trunk and proximal strength (Alejaldre et al., 2012; Chan et al., 2016; Wokke et al., 2008) could contribute to lumbar spine pain, often reported in individuals with LOPD (Alejaldre et al., 2012; Chan et al., 2016). The heterogeneity of pelvic motion

seen in our cohort supports the varied nature of muscle atrophy noted in studies such as that by Figueroa-Bonaparte et al (2016).

Posterior thoracic lean was another common walking characteristic of individuals with LOPD to help overcome deficiencies in trunk and pelvic strength (Chan et al., 2016; Hagemans et al., 2005; Schüller et al., 2012). However, our findings do not support this previous description, rather some individuals with LOPD expressed an anterior lean whilst others walked with a posterior lean or neutral position (see supplementary material). Posterior thoracic lean was previously commonly observed with hyperlordosis of the lumbar region owing to proximal muscular weakness (Chan et al., 2016; Schüller et al., 2012), however, our data cannot confirm this. Future research should explore the lumbar spine posture and motion during walking.

McIntosh et al. (2015) also reported reduced speed and cadence in individuals with LOPD. Compared to this study, LOPD patients who volunteered for McIntosh et al. (2015) demonstrated slower speed and cadence. Other changes such as increased stride width and reduced stride length were also observed unlike the current study, which presented with reduced stride width and no differences in stride length. The individuals who volunteered for McIntosh et al. (2015) study may have had a wider range of disease progression compared to this study. For instance, 6MWT distances reported by McIntosh et al. (2015) ranged from 39.4 to 109.9% of predicted distances, compared to the current study where values of predicted distances were 52.5 – 96.8%. Six-minute walk test indicates exercise tolerance (Chetta et al., 2006; Gibbons, Fruchter, Sloan, & Levy, 2001) and has shown to reduce with the progression of late-onset Pompe disease in association with reduced strength and respiratory capacity (Favejee et al., 2018; Schüller et al., 2012; Wokke et al., 2008). Furthermore, inclusion criteria for LOPD patients in this study required individuals to be able to walk unaided for 50 m. However, McIntosh et al. (2015) recruited individuals who were able to walk at least 10 m with or without a walking aid, with 50% of participants using a walking aid during their study. As the disease progresses, walking and ventilatory aids are often prescribed as a result of the progressive muscle weakness and respiratory impairments (Wokke et al., 2008), therefore likely to affect the spatiotemporal parameters.

In this study, GPS and MAP for the LOPD group were higher compared to the healthy group. Higher GPS and MAP indicates reduced gait quality and presence of gait abnormalities which are likely to lead to greater energy expenditure and reducing functional capacity and quality of life (Scalzo, Flores, Marques, Robini, & Teixeira, 2012).

However, GPS for the LOPD group were not as severe as values previously reported in other pathologies often associated with gait abnormities. For example, the overall GPS in LOPD (7.9°) is lower than that for the mildest (GMFCS I) children with cerebral palsy (8.1°; Baker et al., 2012). As previously stated, individuals were included if they could walk unaided for 50 m, however, as the disease progresses gait quality is likely to reduce owing to the associated progressive muscular weakness.

Greater variance, demonstrated by larger standard deviations, for walking gait patterns were observed individuals with LOPD compared to healthy individuals. Figures in the supplementary data further demonstrate the variability between individuals with LOPD. GPS values ranged from 5.7 – 11.8˚ demonstrating the varied degrees of deviations in the LOPD group, and some patients could be considered within normal ranges for GPS. Although there are reported commonalities with clinical characteristics of LOPD in individuals, the spectrum of these characteristics is broad (Chan et al., 2016; Schüller et al., 2012). Our findings reflect this broad phenotypic spectrum where walking function varies within our sample. Therefore, approach to treatment should consider the commonly observed proximal weakness and reduced control that develops into a myopathic gait as well as provide individual approach. Assessing gait using instrumented gait analysis can provide a valuable evaluation for both clinical and research purposes. The use of GPS can provide a holistic understanding of an individual's gait quality and could provide a useful measure for assessing the efficacy of interventions in this population on walking function given the variability in gait deviations observed.

To our knowledge, this is the first study to analyse walking gait patterns in individuals with LOPD using three-dimensional analysis. Although the sample size could be considered small, when considering the population of LOPD worldwide and estimates of LOPD (approximately 200 diagnosed) in the UK, we are likely to have sampled approximately 6% of the LOPD population within the UK from one of only six adult UK metabolic services and likely a larger percentage of the individuals who passed the eligibility criteria to undertake the study. The variability in gait deviations reported in this study are likely to be a result of the variability within our sample, yet, heterogeneity of our sample reflects the nature of the disease and previous MRI and clinical studies and allows generalisability of findings within the LOPD population. Longitudinal MRI studies have shown progressive atrophy of proximal muscles which are likely to further exacerbate the common characteristics we observed, however, the cross-sectional design of the study limits the ability to understand the change in gait quality as the disease progresses. Therefore, further research is needed to explore the effect of

disease progression and associated disease impairment (muscular weakness) on gait quality. Furthermore, understanding strength capabilities within our sample using a physical examination would have enabled a greater understanding of the compensatory gait patterns observed. It is understood that walking speed influences both kinematics and kinetics (Samson et al., 2001; Schwartz et al., 2008; Swinnen et al., 2013). We accounted for the influence of walking speed in our statistical approach and therefore differences in walking characteristic were beyond differences expected as a result of slower walking speeds. Our study did not assess differences in walking patterns between male and females who had LOPD. There is some evidence to suggest that females are likely to have better walking performance compared to males (i.e. a higher proportion of females walk with a more typical gait) (Favejee et al., 2018) however, this was cross-sectional study and therefore would be difficult to draw predictive conclusions. To our knowledge there is limited evidence exploring differences in strength and walking characteristics between males and females who are diagnosed with LOPD. This could warrant exploration in future studies however the aim of our study was to identify whether there were any common gait characteristics and not to explore male and female differences, which would require a larger sample, possibly as a multicentre study.

Our study demonstrated that gait analysis is sensitive to walking abnormalities in individuals with LOPD. As well as observing common gait characteristics it was also evident that variability in gait deviations were apparent and reflective of the heterogeneity of symptoms in those with LOPD. Gait analysis could work as an adjunct tool to support planning and monitoring of personalised care for individuals with LOPD. GPS and MAPS provides an indication of walking gait performance and could be used to assess the effectiveness treatments such as pharmaceutical treatments or exercise rehabilitation in future clinical trials.

5. Conclusion

Our findings support the presence of a myopathic gait owing to reduced proximal control. However, characteristics such as posterior thoracic lean and either an anterior or posterior pelvic tilt were not apparent as previously suggested. Individuals with LOPD walked slower and with reduced cadence compared to their healthy counterparts. It is likely that muscle weakness, often reported in LOPD patients, leads to reduced walking speed and altered gait patterns. Although our findings demonstrate some common gait characteristics for individuals with LOPD, greater group variance observed should be considered when orientating physiotherapy treatment. Gait deviations reported in the

individuals with LOPD could affect energy expenditure and result in more fatigue, impacting on functional ability.

6. Conflict of Interest

The authors declare that there is no conflict of interest regarding the content of this article.

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9. Tables and Captions

Table 1: LOPD group characteristics

Participant number	Gender	Age at diagnosis (years)	Age at assessment (years)	6MWT (%)
1	M	25	26	64.3
2	M	41	46	60.8
3	M	57	59	77.0
4	F	38	42	72.3
5	F	42	42	96.8
6	M	25	28	55.8
7	F	35	51	72.1
8	M	3	18	52.5
9	F	45	58	91.6
10	M	51	51	58.6
11	F	64	67	56.9
12	F	46	48	65.4

6MWT – 6-minute walk test

573 **Table 2: Kinematic outcome measures**

	Healthy Group	LOPD group	*Adjusted differences[a] (95% CI)*	*P-value*
Maximum thoracic forward lean (º)	3.97 (2.78)	5.53 (5.24)	2.94 (-1.03, 6.91)	.139
Thoracic sway (º)	3.06 (.75)	6.00 (2.53)	2.86 (1.26, 4.45)	.001*
Maximum pelvic tilt (º)	13.88 (4.61)	13.14 (5.78)	0.04 (-5.10, 5.17)	.989
Pelvic tilt range of motion (º)	3.41 (0.90)	6.05 (1.83)	2.39 (1.00, 3.78)	.002*
Contralateral pelvic drop (º)	3.95 (2.35)	5.87 (3.33)	2.18 (-0.57, 4.93)	.114
Maximum hip flexion (º)	35.13 (6.62)	35.28 (6.81)	1.97 (-4.34, 8.28)	.523
Maximum hip adduction (º)	6.99 (4.04)	10.93 (3.91)	4.16 (0.15, 8.16)	.043*
Maximum knee flexion (º)	41.01 (6.28)	38.98 (7.07)	1.38 (-3.82, 6.58)	.586
Maximum knee adduction (º)	2.04 (2.85)	-0.17 (2.86)	-0.27 (-1.66, 1.12)	.692
Maximum ankle dorsiflexion (º)	14.97 (2.73)	15.38 (3.59)	-1.11 (-0.90, 0.38)	.378
Foot progression (º)	-15.15 (4.19)	018.75 (6.44)	-0.82 (-5.60, 3.96)	.725

574 *** Denotes significant difference between LOPD group and healthy group. [a]Adjusted differences and**
575 **confidence intervals (CI) following weighted least squared linear regression**

576

577 **Table 3: Kinetic outcome measures**

	Healthy Group	LOPD group	*Adjusted differences*[a] *(95% CI)*	*P-value*
Maximum hip extensor moment (Nm/(BW*Ht)%)	4.86 (.92)	3.12 (1.30)	-1.22 (-1.84, -0.60)	.001*
Maximum hip abductor moment (Nm/(BW*Ht)%)	4.95 (1.25)	5.23 (0.84)	0.12 (-0.95, 1.19)	.814
Maximum hip absorption power (W/(BW*Ht)%)	-3.94 (1.67)	-3.58 (1.64)	0.42 (-1.19, 2.03)	.592
Maximum hip generation power (W/(BW*Ht)%)	7.10 (1.95)	4.71 (1.42)	-1.46 (-2.88, 0.03)	.046*
Maximum knee extensor moment (Nm/(BW*Ht)%)	3.67 (.97)	3.22 (1.17)	0.53 (0.05, 1.00)	.031*
Maximum knee abductor moment (Nm/(BW*Ht)%)	3.67 (.97)	3.08 (1.50)	0.39 (-0.20, 0.98)	.182
Maximum knee absorption power (Nm/(BW*Ht)%)	-4.90 (2.48)	-2.50 (1.46)	0.42 (-0.86, 1.71)	.499
Maximum knee generation power (Nm/(BW*Ht)%)	3.81 (1.69)	3.14 (1.16)	.02 (-1.28, 1.32)	.976
Maximum ankle plantarflexor moment (Nm/(BW*Ht)%)	8.44 (0.72)	8.20 (.76)	-0.15 (-0.88, 0.57)	.669
Maximum ankle generation power (W/(BW*Ht)%)	19.38 (3.27)	18.22 (3.90)	0.73 (-2.48, 3.94)	.641
First vertical force peak (BW)	1.09 (.06)	1.02 (.05)	-0.03 (-0.07, 0.02)	.252
Second vertical force peak (BW)	1.13 (.05)	1.10 (.05)	-.001 (-0.05, 0.05)	.958

578 *** Denotes significant difference between LOPD group and healthy group. [a]Adjusted differences and**
579 **confidence intervals (CI) following weighted least squared linear regression**

580 **Table 4: Temporal and spatial gait measures for the healthy and LOPD groups**

	Healthy Group	LOPD group	*P-value*
Speed (m/s)	1.3 ± 0.2	1.1 ± 0.1*	.039
Stride length (m)	1.3 ± 0.1	1.3 ± 0.2	.410
Stride width (cm)	12.6 ± 2.3	9.9 ± 3.8*	.048
Cadence (steps/ min)	113 ± 7	105 ± 7*	.008
Step length (m)	0.7 ± 0.1	0.6 ± 0.1	.443
Stance time (%)	60.5 ± 3.3	62.3 ± 3.6	.443

581 *** Denotes significant difference between LOPD group and healthy group**

10. Figure Captions

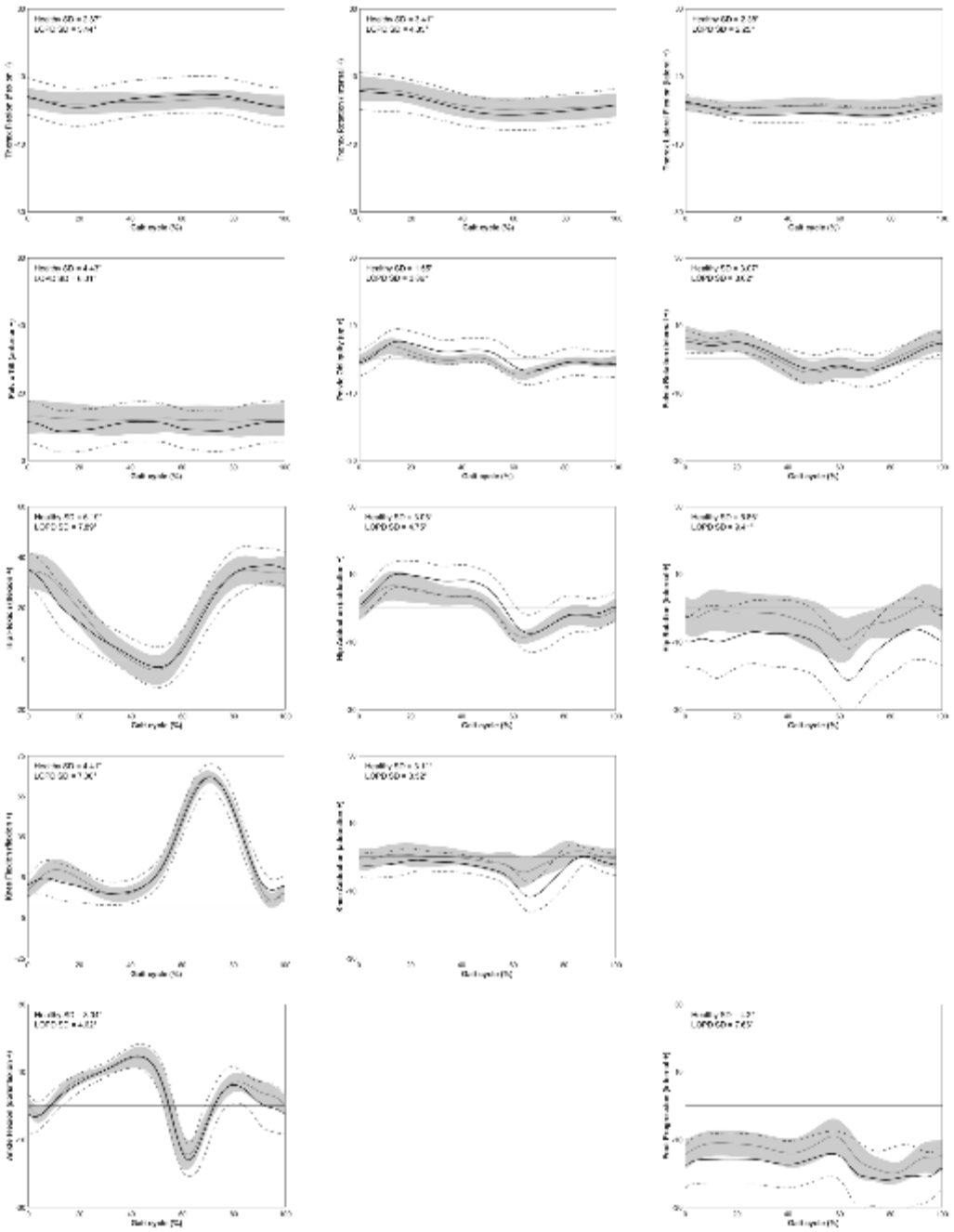


Fig 1: Left side means and standard deviations kinematic gait curves for the LOPD group (black) and healthy group (grey). Standard deviations (SD) across the waveform are denoted for each group.

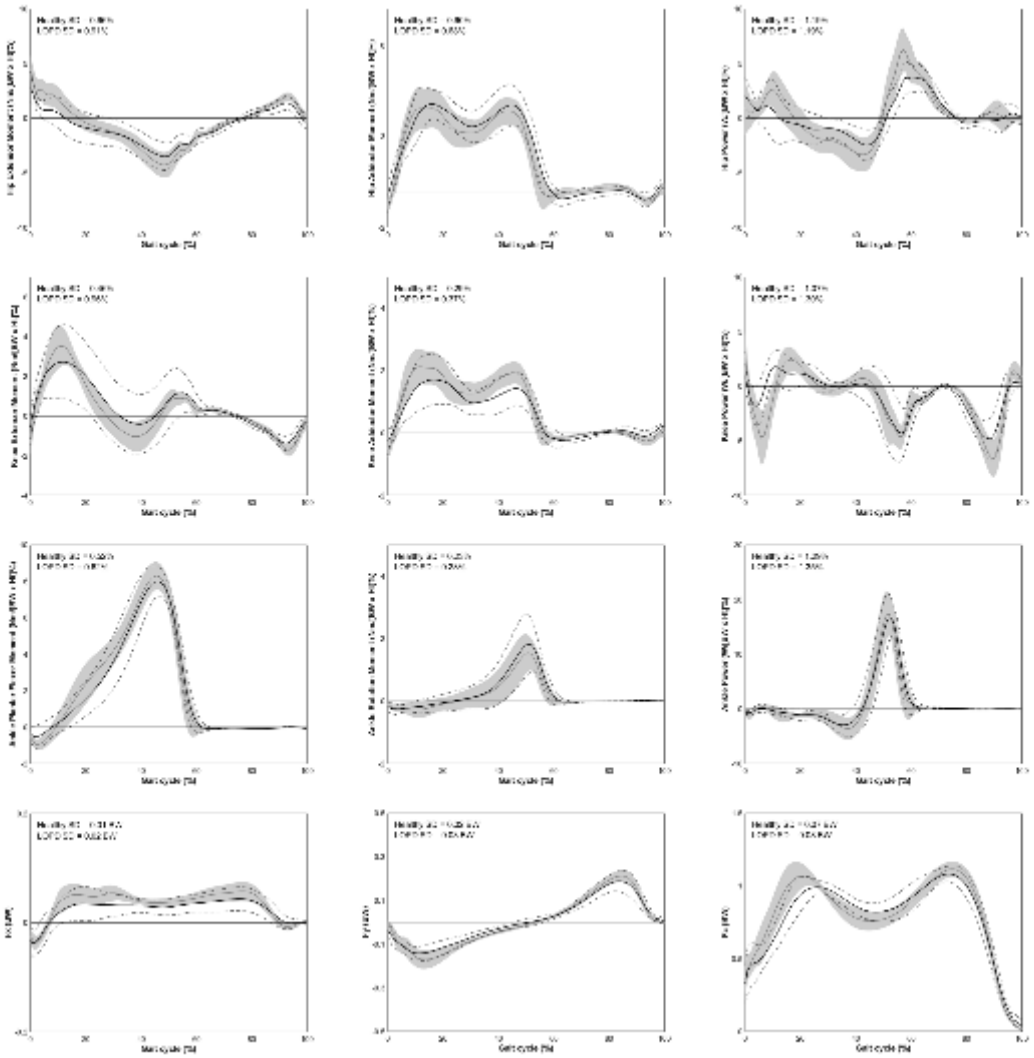
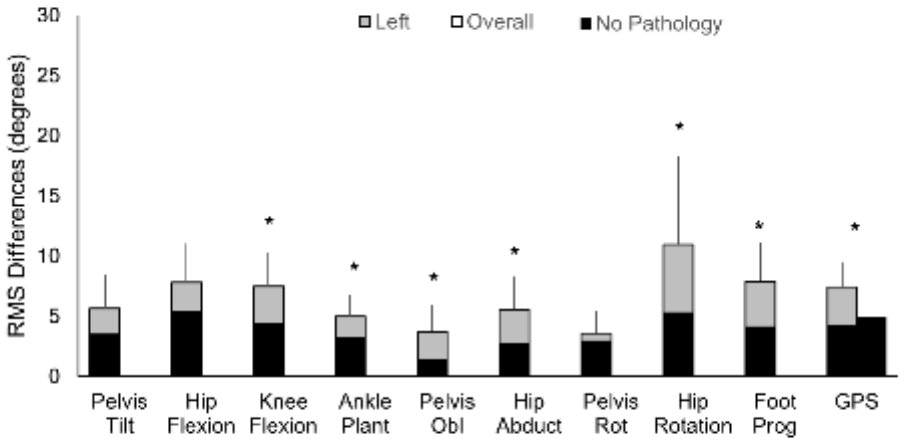


Fig 2: Left side means and standard deviations kinetic gait curves for the LOPD group (black) and healthy group (grey). Standard deviations (SD) across the waveform are denoted for each group.



597

598 Fig 3: The movement analysis profile for the LOPD group for the left side (grey)
599 compared to the healthy group with no pathology (black). GPS for left side (grey) and
600 overall (white) gait pattern are displayed in the rightmost column. * Denotes a significant
601 difference (p<0.05) between groups.