Physiotherapy Management in Adults with Pompe Disease

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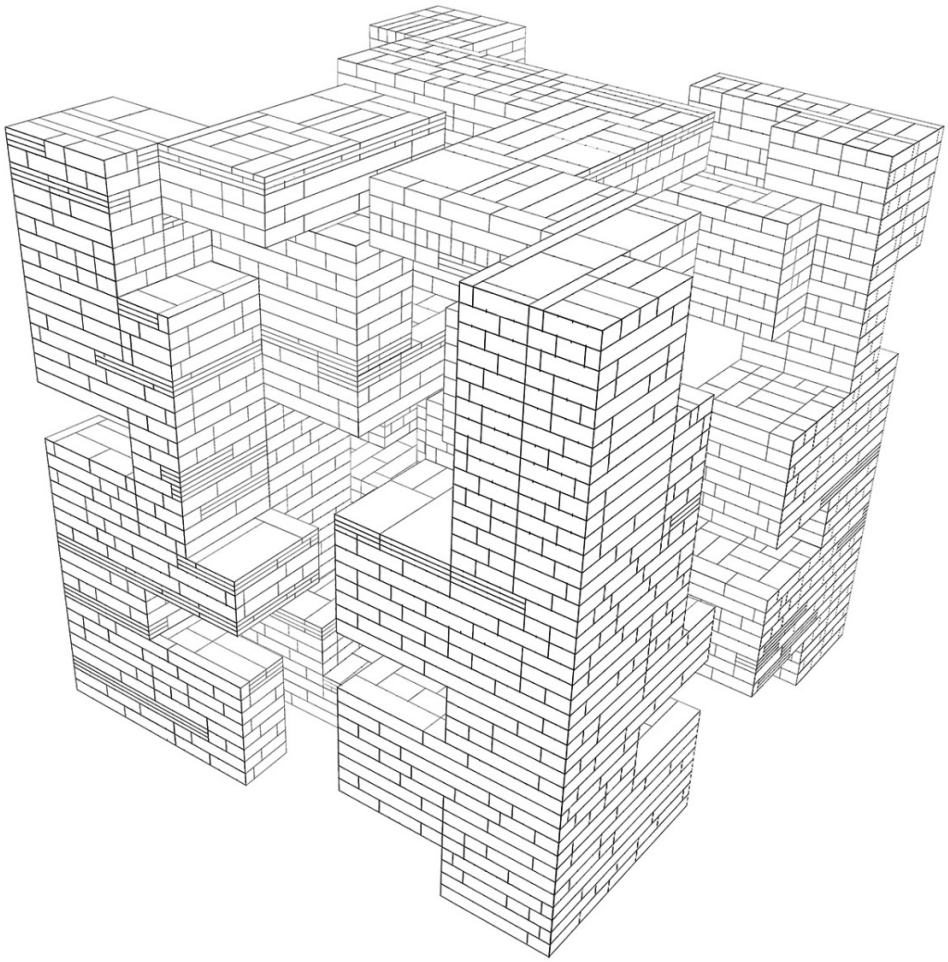
Table of contents



CHAPTER 01

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

Pompe disease, also referred to as glycogen storage disease type II or acid maltase deficiency, is an autosomal recessive, progressive, debilitating disease. This neuromuscular disorder is characterized by progressive muscle weakness. As part of the disease process, the muscles of the trunk and pelvic girdle start to become affected first and gradually the disease process spreads from the proximal to the distal muscles of the legs and arms. The muscles of the hands and feet are relatively spared until late in the disease process. The respiratory muscles, which include the diaphragm, are involved as well. The emerging mobility and respiratory problems have a great impact on daily functioning and quality of life of patients with Pompe disease.

Pompe disease was the first neuromuscular disorder for which disease specific treatment became available. The introduction of enzyme replacement therapy (ERT) with recombinant human alfa-glucosidase (the enzyme deficient in Pompe disease) has improved the prospects of patients. With the growing attention for Pompe disease the role of physiotherapy also became more prominent. Physiotherapy not only plays an important role in identifying and quantifying motor and functional limitations and recommendation of appropriate adjuvant physiotherapeutic interventions, but in the monitoring of disease progression and evaluation of the effect of enzyme replacement therapy and physiotherapeutic intervention as well.

This introductory chapter provides background information on Pompe disease with regard to its pathology and clinical manifestations, and describes the role of physiotherapy in the treatment of patients with Pompe disease.

01

POMPE DISEASE

Pompe disease derives its name from the Dutch pathologist JC Pompe, who described the disease in 1932. He reported a case of a 7 month-old girl who died of cardiomyopathy [1]. The disease was identified as a glycogen storage disorder, later named as glycogen storage disease type II, in which glycogen had accumulated within vacuoles of all examined tissues, including skeletal muscles. Glycogen is an important source of energy primarily in the cells of the liver and skeletal muscle. In the degradation and synthesis of glycogen many enzymes are involved. Deficiencies of these enzymes can lead to abnormal glycogen metabolism, and as a consequence a glycogen storage disorder may develop. In 1963 Hers identified acid α-glucosidase (GAA), the enzyme which is responsible for the breakdown of glycogen in the lysosome, and reported its absence in tissue samples of five patients suffering from Pompe disease [2]. Pompe disease is a glycogen storage disorder and also belongs to a group of diseases known as the lysosomal storage disorders.

PATHOGENESIS AND PATHOPHYSIOLOGY

In general, lysosomal storage disorders (LSDs) are diseases in which the lysosomal function is impaired due to a deficiency of a lysosomal enzyme leading to accumulation of the macromolecules it should degrade. In Pompe disease the lysosomal dysfunction is provoked by the absence or deficiency of the enzyme acid α-glucosidase. Pathogenic sequence variations in the gene coding for GAA, which is located on chromosome 17, can result in GAA protein not being produced at all, abnormal processing of GAA or reduced amounts or normal GAA. The c.-32-13T>G splice site variation is the most common sequence variation among Caucasian children (60%) and adults (>80-90%) with Pompe disease. The c.-32-

13T>G leads to variable splicing with production of 10-20% normal GAA protein and residual GAA activity and anon-classic or late onset presentation. Most patients who took part in the studies described in this thesis carry the c.-32-13T>G on one allele. Pompe disease inherits in an autosomal way; both GAA alleles need to carry a pathogenic sequence variation for the disease to manifest.

Glycogen metabolism is regulated bij various enzymes. GAA is needed for the breakdown of glycogen that has entered the lysosome through autophagy. Normally, glycogen gets degraded to glucose in the lysosome by GAA . Deficiency of this enzyme leads to continuous accumulation of lysosomal glycogen, resulting in an increase of lysosomes in size and number, loss of their function and rupture, followed by cellular damage. This process can be found in virtually all cells of the body, but the effects are most notable in muscle cells [2, 3].

The pathophysiology of muscle damage and the reduction in mechanical performance of muscles is not fully understood in Pompe disease. Accumulation of lysosomal glycogen leading to the aforementioned cascade may cause mechanical loss of contractility resulting in muscle weakness [4, 5]. A second hypothesis is that autolytic enzymes, released from ruptured lysosomes, are involved in muscle damage and wasting [6]. The autophagic buildup containing cellular debris representing a huge non-contractile inclusion in the diseased muscle fibers may also contribute to the muscle weakness [7]. Further, it has been shown that satellite cells, which are essential for muscle regeneration are unable to prevent progressive muscle wasting due to insufficient satellite cell activation [8].

PRESENTATION, CLINICAL SPECTRUM AND DIAGNOSIS

Pompe disease is a rare disease. In the Netherlands, its overall incidence is 1 in 40,000 births [9]. The disease can manifest at any age and with varying symptoms resulting in a continuous spectrum of disease phenotypes [10]. This spectrum ranging from a severe, rapidly progressive classic-infantile form to more slowly progressing phenotypes that can manifest from early childhood to late adulthood [11, 12]. There is an association between these phenotypes and α-glucosidase activity, but secondary genetic and environmental factors may play a role as well. [13, 14].

The classic-infantile form of Pompe disease presents shortly after birth, at a median age of 1.6 months (range 0-6.8) [12]. These infants usually have hardly any GAA activity. The disease is rapidly progressive and characterized by hypertrophic cardiomyopathy and extreme hypotonia. Patients are unable to achieve motor milestone and patients die from cardiorespiratory failure in the first year of life in the absence of treatment [10, 12, 15].

Onset of symptoms in patients with non-classic disease may range from the first to the sixth decade of life. These patients have some residual acid α-glucosidase activity. Patients have a gradual developing proximal myopathy, which typically fits a pattern of limb-girdle diseases. It causes both mobility and respiratory problems and eventually leads to wheelchair and/or ventilator dependency, with respiratory failure as the main cause of death. This thesis will focus on adult patients with non-classic Pompe disease.

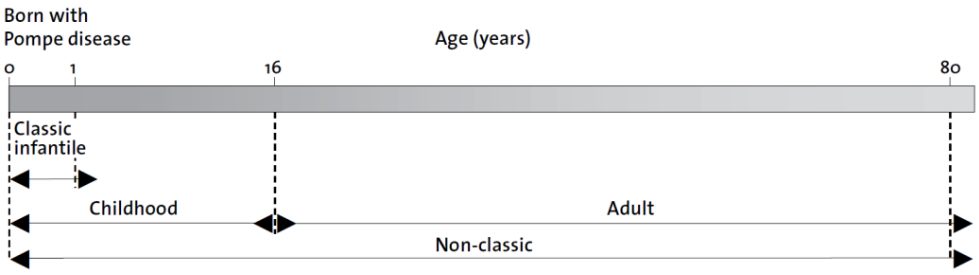


Figure 1 | The clinical spectrum of Pompe disease

This figure was adapted from Güngor and Reuser. How to describe the clinical spectrum in Pompe disease? Am J Med Genet A 2013; 161A(2):399-400, by permission of John Wiley and Sons.

Diagnosing Pompe disease is often difficult due to the heterogeneous clinical presentation, the overlap of symptoms with other neuromuscular diseases and the relative rarity of the disease. The diagnosis of Pompe disease can be established by demonstrating deficiency of acid-α-glucosidase activity in leukocytes, fibroblasts or skeletal muscle and/or genetically by mutation analysis [16].

THE HEALTH CONDITION OF PATIENTS WITH POMPE DISEASE ACCORDING TO THE ICF MODEL: IMPAIRMENTS, LIMITATIONS IN ACTIVITY AND RESTRICTIONS IN PARTICIPATION

The International Classification of Functioning, Disability and Health (ICF) of the World Health Organization (WHO) [17] provides a framework to describe a health condition of a patient, which incorporates the biological, individual and social

elements that affect health. In this model, as illustrated in Figure 2, a health condition or disease can be described multidimensional by the problems at the body or organ level, those with execution of tasks (activity), and by restrictions in participation in daily life. All components of this model are important and may interact with another.

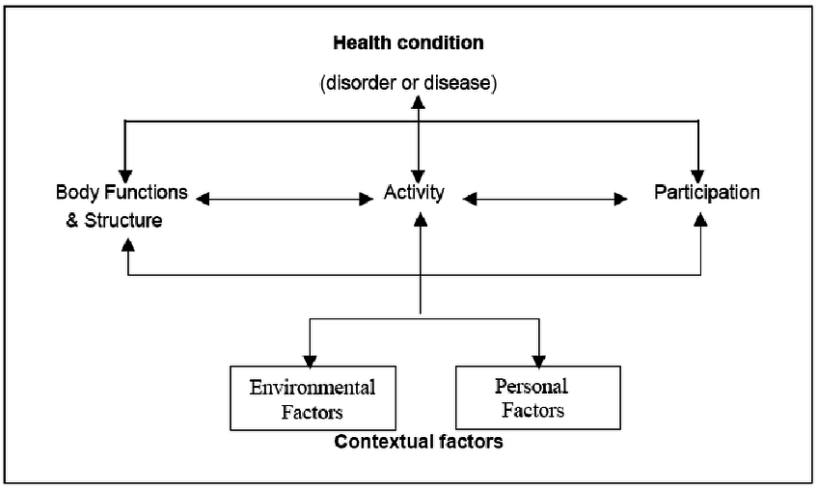


Figure 2| ICF model

This figure was adapted from the World Health Organization, 2001

BODY FUNCTIONS & STRUCTURE LEVEL

At the body and organ level, Pompe disease is characterized by a slowly progressive symmetrical myopathy, starting from the trunk with early involvement of paravertebral and abdominal muscles, and gradually moving to the extremities [18-21]. Data from the international registry showed that proximal muscle weakness was observed in the lower extremities in 89% of adult patients and in the upper extremities in 73%; weakness of the trunk was observed in 65% [13]. Figure 3 gives a schematic overview of the muscles that are affected in adult patients with Pompe disease, and the severity of the weakness [11].

Finally, selective muscle weakness in the extremities leads to coordination problems, axial muscle weakness to impaired core stability and posture problems (i.e. scoliosis and increased lumbar lordosis) and scapula alata, which is reported in one third of the adult population [11, 22]. Less familiar features of Pompe disease are bulbar weakness, ptosis and incontinence. Incontinence has been associated with glycogen accumulation in both smooth muscle fibers of the bladder and intestine [23, 24] and skeletal muscles of the pelvic floor [18, 21].

Also the respiratory muscles and diaphragm are affected in Pompe disease, with the diaphragm being by far the most impaired muscle [25, 26]. This results in reduced pulmonary function. A cross-sectional study in Dutch adult patients showed that 79% of the patients had some degree of pulmonary dysfunction [27], leading to dyspnoea with exertion or when supine and impaired cough. Altogether, the skeletal muscle weakness and respiratory problems can lead to decreased endurance.

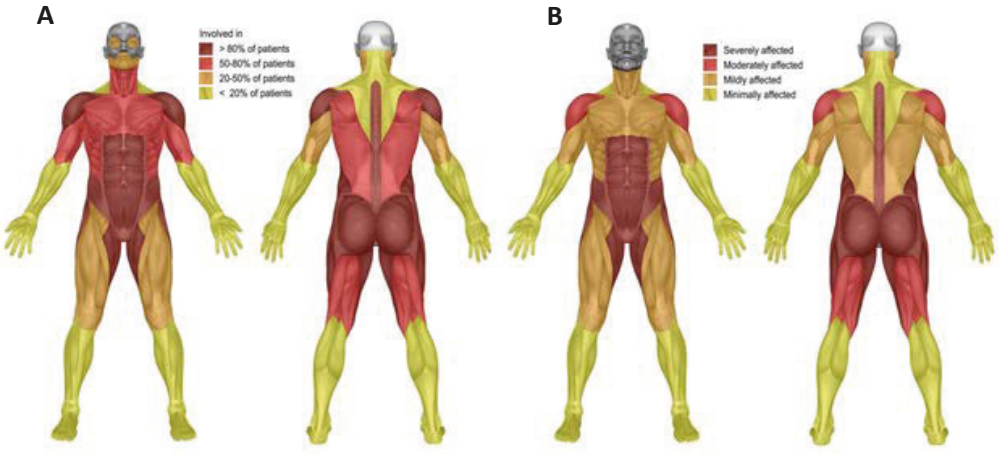


Figure 3| Distribution (A) and severity (B) of muscle weakness in adults with Pompe disease.

This figure was adapted from van der Beek et al. Clinical features and predictors for disease natural progression in adults with Pompe disease: a nationwide prospective observational study. Orphanet J Rare Dis 2012;7:88, by permission of BioMed Central.

Finally, pain and fatigue are reported by adult patients with Pompe disease. Nearly one in two Dutch patients reported having experienced pain in the previous 24 hours [28]. This was most frequently reported in the shoulder region, back and the upper legs, and was described as exhausting (70%) or pulling/tearing (57%). Both postural problems and muscle pain might be underlying mechanisms [29]. Fatigue is highly prevalent among both mildly and severely affected adult patients with Pompe disease. [30, 31]. It has been reported that 79% of the patients receiving ERT were fatigued and 55% severely fatigued.

ACTIVITY LEVEL

Due to muscle weakness of the trunk and limb-girdle, patients experience gradual difficulty with motor function, noted initially in problems with walking and running [22]. It can also limit performance of activities of elevation against gravity such as climbing stairs, getting up out of a chair, and lifting the arms overhead [22, 32, 33]. The majority of patients with Pompe disease (8 out of 10) experience problems with walking [22, 33], varying from imbalance to compensatory movement patterns such as Duchenne or Trendelenburg signs or a swayback posture. Eventually, these problems will lead to dependency of walking aids and, ultimately, patients will lose the ability to walk and become wheelchair dependent.

PARTICIPATION LEVEL

Pompe disease has a large impact on the level of participation of patients in life [34]. The loss of the ability to walk hampers daily activities such as domestic tasks, work and outdoor leisure activities. Reduced respiratory functioning, pain, fatigue and incontinence will further add to this.

Quality of life has been shown to be significantly affected in adult patients [22, 34]. The physical health status appears to be less than that of people in the general population [16, 35], where wheelchair use is associated with lower physical and social functioning scores, and the use of artificial ventilation with lower physical scores [35]. Paradoxically, the mental-health status of patients with Pompe disease was found not be reduced. Is might be due to better coping strategies patients developed over time. Personal factors influence how a disease and/ or disability is experienced.

Also environmental factors play an important role in people's functioning. These factors range from physical factors (such as climate, terrain or building design) to social factors (such as attitudes, institutions, and laws)[17]. The aforementioned impairments, limitations in activity, and restrictions in participation that often accompany Pompe's disease can be displayed in the ICF model as follows (see figure 4).

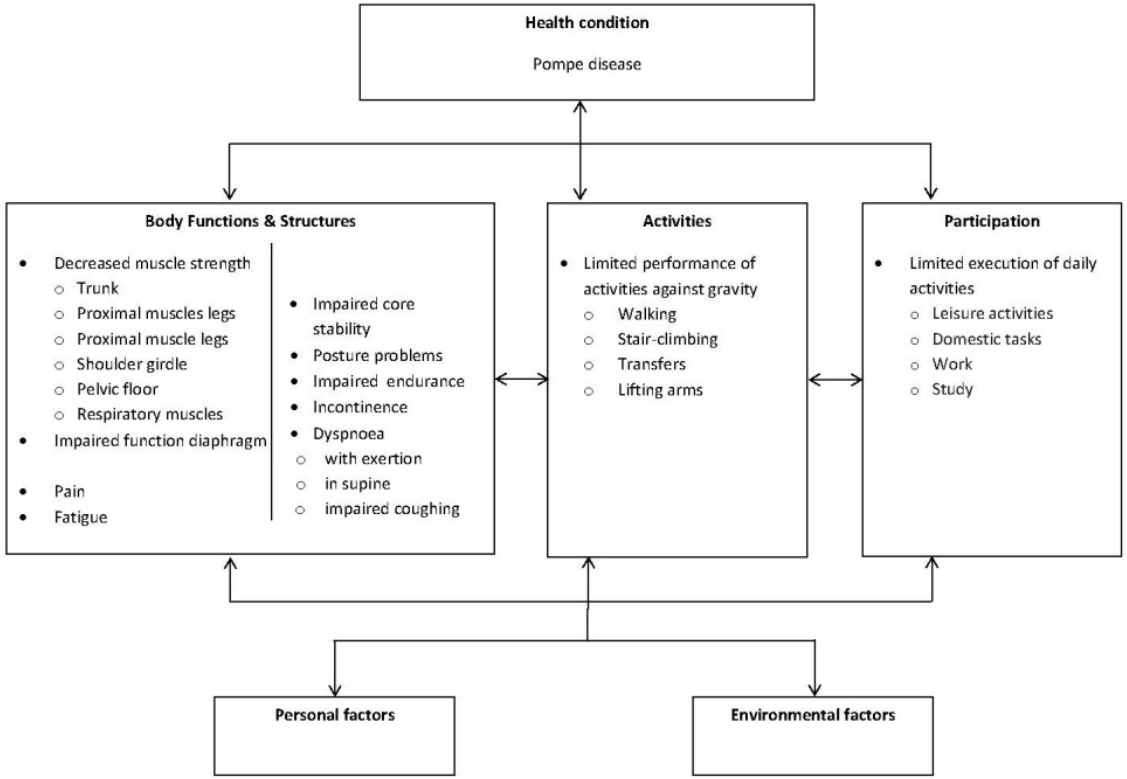


Figure 4 | ICF-model: Overview of health problems that often accompany Pompe's disease and the factors that can influence these problems

CURRENT THERAPEUTIC APPROACH

Since 2006, enzyme replacement therapy (ERT) with recombinant human acid α-glucosidase has been approved for the treatment of Pompe disease. Several studies in children and adults have shown effects of ERT on walking distance, pulmonary function, muscle strength and muscle function and on survival [36-39]. However, the results also suggest that there is a large variation in the effects of treatment in these patients. Improvement of the remaining functional impairments of these patients is still desired. Physiotherapy to advance physical functioning of patients might be beneficial in this.

PHYSIOTHERAPY IN POMPE DISEASE

Physiotherapy (PT) tries to influence impairments of the musculoskeletal system and promotes mobility and function by using mechanical force and movements, manual therapy, exercise therapy, and electrotherapy. It encompasses both examination, diagnosis, prognosis, monitoring and physical intervention. It has a clear role in treating symptoms of acute diseases and its role in treating symptoms of chronic diseases is also well recognized. In patients with neuromuscular disorders one of the primary questions is whether exercise training may be helpful, and in which form (i.e. aerobic and/or progressive resistance) [40]. For a long time, exercise training was thought to be harmful in patients whose muscles were affected by a neuromuscular disease (NMD), although there was no corroborating data. Because affected muscles are already functioning close to its maximal limits, exercise training, was for a long time considered to be harmful to this damaged muscle tissue. In recent years, however, exercise programs have been shown to have a positive effect on muscle strength and endurance of patients with NMDs with a similar presentation as Pompe disease, such as facioscapulohumeral muscular dystrophy and limb girdle dystrophy [41].

When it comes to Pompe disease, a few studies had been conducted. These reported an improvement or stabilization in muscle strength with aerobic exercises, either combined with strengthening exercises or a high-protein diet [42-45]. Due to the rarity of the disease, these studies were limited by small numbers. Furthermore, the type of exercises used and their intensity and duration varied. In order to strengthen the evidence for exercise training, a study needed to be performed in a larger population of adults with Pompe disease. Moreover, this could be the starting point for developing guidelines for clinical practice.

A limitation of exercise training is that it mainly focuses on the ICF level of body functions and structures, while patients also experience limitations at the activity level [22]. Physiotherapeutic care focuses on all levels of the ICF model. Besides maintaining and optimizing bodily functions it also teaches patients to deal with limitations at the activity and participation level. Furthermore, the ICF model considers human functioning as an intricate interplay between all three levels as well as with personal and environmental factors. Understanding how these levels work together could help physiotherapists to focus their treatments better. For example, it would be helpful to have insight into the extent to which activities, such as walking performance, can be explained by variables on the other levels of the ICF model. As patients with Pompe disease have indicated that they consider walking performance to be the most restricted activity in daily life [22], it would make sense to start with unravelling the determinants of walking performance.

Exercise training can be focused on improving a patients' functioning in general, or be more specifically focused on a few specific muscles or functions, like walking. Such targeted exercises of specific muscles can also be effective in treating other symptoms related to Pompe disease, such as incontinence or respiratory function. Incontinence has been reported as a problem in Pompe

disease [46-48], but its occurrence in the Dutch Pompe population is unclear. Pelvic floor physiotherapy (PFPT) addresses (amongst others) specific weakness of the pelvic floor muscles and could be beneficial for Pompe patients suffering from incontinence. However, like generic physiotherapy, pelvic floor physiotherapy is a relatively unknown treatment option in patients with Pompe. At present there is no evidence of the added value of pelvic floor physiotherapy in Pompe patients, although this has been shown for the general population.

AIMS AND OUTLINE OF THIS THESIS

This thesis comprises a number of studies aimed to investigate whether physiotherapeutic care of patients with Pompe disease can be a valuable addition to the existing enzyme replacement therapy.

Chapter 2 and 6 provide an overview of the contemporary physiotherapy practice, both regular and specifically aimed at the pelvic floor muscles, in adult patients with Pompe disease in the Netherlands. **Chapter 3** and **4** report on the feasibility and safety performing a standardized and well-structured exercise program combining aerobic, resistance and core stability exercises adjunct to enzyme replacement therapy. Whereas **chapter 3** focuses on endurance, muscle strength, core stability and functional activity is the focus in **chapter 4** on fatigue, pain, physical and mental functioning. In **chapter 5** we study factors that influence walking performance in adult patients with Pompe disease, including muscle strength, BMI and ventilator dependency. **Chapter 6** focuses on the prevalence and characteristics of incontinence in Dutch adult patients with Pompe disease. The general discussion, **chapter 7**, gives an on overview of the results and outline directions for future research in the field of physiotherapy in Pompe disease.

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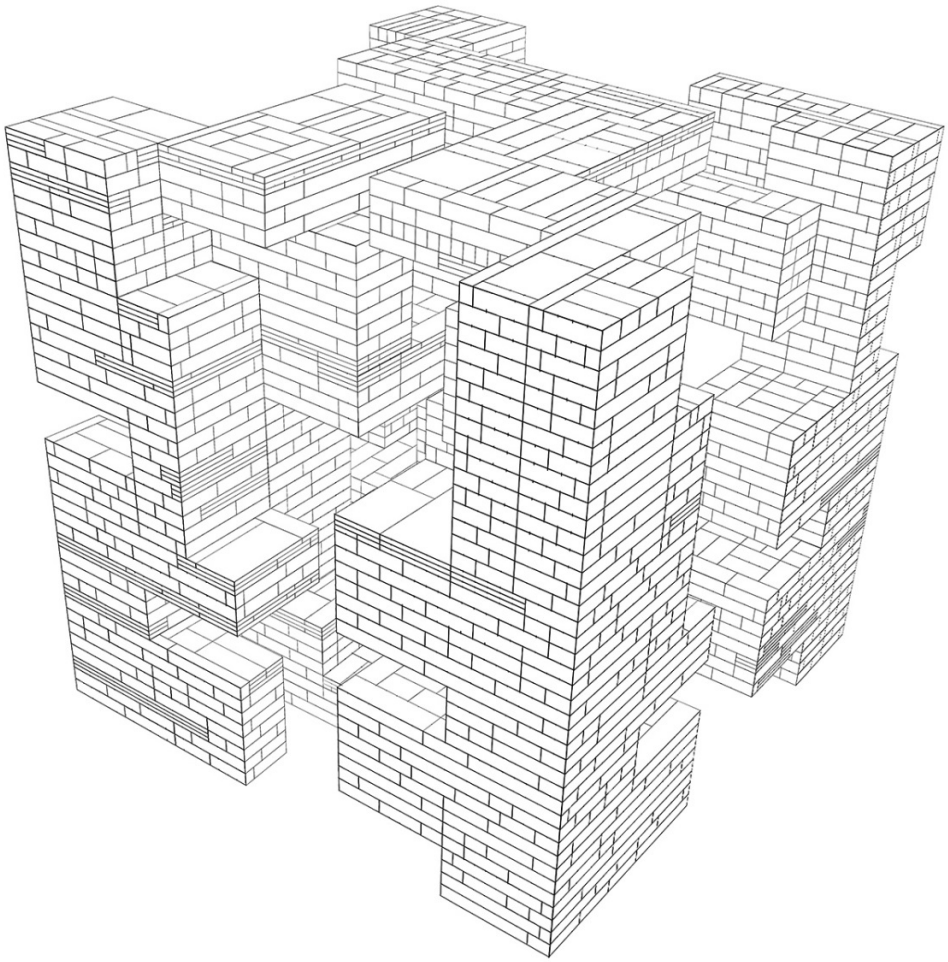

CHAPTER 02

PHYSIOTHERAPY MANAGEMENT IN LATE-ONSET POMPE DISEASE:

CLINICAL PRACTICE IN 88 PATIENTS

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ABSTRACT

Pompe disease is an inherited metabolic, neuromuscular disorder. With the introduction of enzyme replacement therapy skeletal muscle and respiratory function can be stabilized or improved. Additional physiotherapy to advance physical functioning of patients might be beneficial, but evidence and guidelines are lacking.

In order to get an insight into current practices of referral and treatment, and perceived benefit, we performed a survey among 88 Dutch adult Pompe patients and 31 physiotherapists.

Sixty percent of patients were ever referred for physiotherapy, whereas currently less than 40% receive physiotherapy. Approximately 50% of patients were referred for loss of muscle strength; while 74% received muscle strengthening exercises, often combined with aerobic endurance training. In 47% of patients the intervention did not match the referral reason. More than two-thirds of patients and physiotherapists perceived physiotherapy as beneficial, and the majority highlighted the need for guidance.

Physiotherapeutic care can be improved by tailoring interventions to referral reasons and treatment objectives. More high quality studies are urgently needed to assess which interventions are most useful in this patient group.

INTRODUCTION

02

Pompe disease is a neuromuscular disorder caused by a deficiency of lysosomal alpha-glucosidase. Depending on age of onset, it can be classified as an infantile, childhood, or an adult phenotype. The disease presents as a broad clinical spectrum, ranging from severe generalized hypotonia and hypertrophic cardiomyopathy in the infantile form, to a slowly progressive proximal myopathy in late-onset Pompe disease. The proximal myopathy seen in adult patients is mainly related to skeletal muscle dysfunction. It causes both mobility and respiratory problems and eventually leads to wheelchair and/or ventilator dependency. Pompe disease used to be an untreatable disease but the introduction of enzyme replacement therapy (ERT) with human recombinant Alglucosidase alfa (Myozyme®) has improved the prospects of patients. ERT has shown to improve survival and motor outcome in patients with the infantile phenotype [1-3] and to improve walking distance, and stabilize respiratory function in patients with the late onset phenotype[4-6].

Previously a sedentary lifestyle was recommended to prevent overuse of the damaged muscle tissue [7]. In recent years, exercise programs have been shown to have a positive effect on muscle strength and endurance in patients with related neuromuscular disorders (NMD) [8]. In addition, an observational study on the effect of ERT in Pompe patients reported better functional outcomes for those who specifically subscribed to physiotherapy [4]. These promising results together with the advent of ERT have resulted in an increased demand for physiotherapy interventions in Pompe patients.

Despite its assumed added value, scientific evidence for the effectiveness of physiotherapy in Pompe disease is lacking. Consequently, there is no consensus

regarding the most efficient physiotherapy interventions for Pompe disease and guidelines are lacking. As a first step towards the development and evaluation of a physiotherapy program adjunct to ERT it is important to gain insight into the current practices and perceptions.

We conducted a survey among all Dutch late-onset Pompe patients and their therapists to gain insight into the extent of referral to physiotherapy, types of physiotherapy interventions currently being used and their specifications as well as their perceived effect.

MATERIALS AND METHODS

This study took place within the context of a larger study on the natural course and effects of ERT in adult Pompe patients at the Erasmus MC University Medical Center Rotterdam. This is the Dutch national referral centre and an international expert centre for Pompe disease. All patients provided written informed consent.

SUBJECTS

PATIENTS

All 90 adult patients with a confirmed diagnosis of Pompe disease seen in the Erasmus MC between April and August 2009 (i.e. the entire Dutch adult Pompe population known at the time) were included. Of these, 78 visited the outpatient clinic and the 12 remaining patients were contacted by telephone. Two patients were unable to speak by telephone because of invasive ventilation. Therefore, 88 patients were enrolled in this study. The patients were categorized into those ever receiving physiotherapy and those who never received physiotherapy.

PHYSIOTHERAPISTS

Patients who had ever received physiotherapy to treat symptoms related to Pompe disease were asked for permission to contact their therapist. All patients agreed and, subsequently, a questionnaire was sent to their therapists. Eleven out of 52 were not traceable, and 10 did not respond, so finally 31 therapists were included in this study.

MEASUREMENTS

PATIENTS

Using a custom made questionnaire, information on referral (referring specialist, reason for referral or non-referral), perceived effect of the physiotherapy intervention and the need for guidelines was obtained. Patients received the questionnaire during regular history-taking, or over the phone. Information on age, gender, year of first symptoms, year of diagnosis and use of walking aids, wheelchair or ventilator were collected as part of the larger study on Pompe patients in the centre.

PHYSIOTHERAPISTS

Another custom made questionnaire was sent out to the therapists. It covered the same topics as the patients' questionnaire supplemented by questions on objective, type and specifications (frequency, duration, intensity) of interventions, evaluation procedures, and reasons for ending treatment. The type of intervention was divided into seven intervention categories: (1) aerobic exercises, (2) muscle strengthening exercises, (3) respiratory care, (4) mobilization techniques (i.e. maintenance of range of motion), (5) massage therapy, (6) practicing functional tasks (i.e. sit-to-stand transfer) or (7) others.

Both questionnaires consisted of closed-ended questions, with dichotomous or multiple answer options.

ANALYSIS

Demographic data were summarized and the referred and non-referred group compared using Mann–Whitney and chi-square tests as appropriate. Because disease severity may affect the choice of treatment goals and interventions,

responses were compared between mildly affected patients (walking with or without aids and no ventilator use) and moderate to severely affected patients (wheelchair bound and/or ventilator use).

Descriptive statistics were performed with SPSS 16.0 for Windows software (SPSS, Inc., Chicago IL).

RESULTS

PATIENT CHARACTERISTICS

Of the 88 included Pompe patients 32 (36.4%) received physiotherapy for the treatment of symptoms of Pompe disease at time of this study; 20 (22.7%) had received physiotherapy in the past and stopped, and 36 patients (40.9%) had never been referred for physiotherapy. Table 1 presents the characteristics of the included patients. Patients had a median disease duration of 16.5 years (3–53) and 85% of them had started ERT. Those referred to a physiotherapist had a notably longer disease duration and were more dependent on walking aids or wheelchair compared to those who had never been referred ($p = 0.03$ and $p = 0.02$, respectively). On the other hand, inspecting those patients who were independent on walking aids, about half were referred and half never referred (23 and 27 patients, respectively).

Table 1 | Characteristics of Dutch adult Pompe patients (N = 88).

	Total N = 88	**Ever PT N = 52**	**Never PT N = 36**	**P-value***
Gender, male (N (%))	42 (47.7)	23 (44.2)	19 (52.8)	0.430
Age in years (median (range))	53.0 (25–76)	53.0 (29–76)	51.5 (25–74)	0.842
Disease duration in yrs (median (range))	16.5 (3–53)	19.5 (6–45)	13.0 (3–53)	0.030
Mobility (N (%)):				0.02
- no walking aids	50 (56.8)	23 (44.2)	27 (75.0)	
- use of walking aids	14 (15.9)	10 (19.2)	4 (11.1)	
- partial wheelchair use	7 (8.0)	6 (11.5)	1 (2.8)	
- permanent wheelchair use	17 (19.3)	13 (25.0)	4 (11.1)	
Ventilator use (N (%)):				0.170
- no ventilator use	64 (72.7)	35 (67.3)	29 (80.6)	
- non-invasive use	18 (20.5)	12(23.1)	6 (16.7)	
- invasive use	6 (6.8)	5 (9.6)	1 (2.8)	
Physiotherapy (N (%)):				N/A
- never	36 (40.9)	N/A	36	
- at present	32 (36.4)	32	N/A	
- stopped with treatment	20 (22.7)	20	N/A	

PT: physiotherapy, N/A: not applicable.
* P-value for the difference between ever and never treated patients using chi-square test or for age and disease duration, the Mann–Whitney *U* test.

The 20 patients who stopped physiotherapy were significantly more often ventilator dependent than patients who were receiving physiotherapy at the time of this study (50% versus 22%, p = 0.04). There were no significant differences between these groups regarding use of walking aids and disease duration.

REFERRAL CHARACTERISTICS AS REPORTED BY PATIENTS

Most patients had been referred by either their neurologist (49.1%) or general practitioner (23%). Table 2 shows the reasons for referral according to the patients. Overall, the main referral reasons were loss of muscle strength (52%), loss of general condition (40%) and pain (25%). In severely affected patients problems with activities of daily living (ADL) (27%) also played a large role. Twenty-five patients had more than one reason for referral (mean 1.60; range 1 to 3). Muscle weakness and decrease of general condition was the combination most commonly seen (25%).

Table 2 | Reasons for referral to physiotherapy for Dutch adult Pompe patients.

	Total N (%) N = 52	**Mild N (%) N = 30**	**Moderate–severe N (%) N = 22**
Muscle weakness	27 (51.9)	14 (46.7)	13 (59.1)
Loss of general condition	21 (40.4)	13 (43.3)	8 (36.4)
Pain	13 (25.0)	8 (26.7)	5 (22.7)
Problems with ADL	9 (17.3)	3 (10.0)	6 (27.3)
Stiffness	7 (13.5)	4 (13.3)	3 (13.6)
Other	4 (7.7)	2 (6.7)	2 (9.1)
Pulmonary problems	3 (5.8)	1 (3.3)	2 (9.1)

ADL: activities of daily living. More than one reason can be stated so percentages add up to more than 100%.

The most frequent reason (78%, 28/36) for not being referred to physiotherapy was that patients did not experience restrictions in daily life. Two patients were told that physiotherapy was harmful and six patients could not explain why they never received physiotherapeutic care.

TREATMENT CHARACTERISTICS REPORTED BY PHYSIOTHERAPISTS

Patients were treated one to three times per week (median 1) and the duration of one treatment varied from 12 to 60 min (median 30). The median duration of the treatment period was 12 months (range 1–180).

Table 3 shows the main treatment objectives and interventions. The most common treatment goals were to improve muscle strength (81%), walking (68%), and general condition (42%). For each patient the therapists formulated at least two objectives.

Overall, the most frequently used interventions were muscle strengthening exercises (MSE, 74%), aerobic exercise therapy (AET, 68%) and home exercise program (HEP, 68%). The HEP covers a wide range of different exercises performed at home, without supervision of a therapist, and often included mobilization, walking and strengthening exercises. In addition, mobilization techniques and massage therapy (MT, 53%) were frequently used in mildly affected patients for reducing stiffness and pain. Training of activities of daily life (ADL, 67%) was regularly applied in more severely affected patients. Most patients received more than one intervention (mean 2.5; range 1–5), the most common combination being MSE with AET (61%).

Table 3 | Treatment objectives and interventions used, reported by 31 therapists, for mild and moderately to severely affected adult Pompe patients.

Improvement of:	Total N (%) N = 31	Mild N (%) N = 19	Moderate–severe N (%) N = 12
Objectives			
Muscle strength (BL)	25 (80.7)	15 (78.9)	10 (83.3)
Walking (AL)	21 (67.8)	12 (63.2)	9 (75.0)
General condition (BL)	13 (41.9)	8 (42.1)	5 (41.7)
STS (AL)	10 (32.3)	7 (36.8)	3 (25)
Muscle coordination (BL)	9 (29.0)	6 (31.6)	3 (25.0)
Stair climbing (AL)	9 (29.0)	9 (47.4)	0 (0.0)
Other (AL)	8 (25.8)	5 (26.3)	3 (25)
Stiffness (BL)	7 (22.6)	4 (21.1)	3 (25.0)
Standing (AL)	7 (22.6)	3 (15.8)	4 (33.3)
Pain (BL)	5 (16.1)	4 (21.1)	1 (8.3)
Pulmonary status (BL)	3 (9.7)	2 (10.5)	1 (8.3)
Other (BL)	3 (9.7)	2 (10.5)	1 (8.3)
Cycling (AL)	2 (6.5)	2 (10.5)	0 (0.0)
Sitting (AL)	2 (6.5)	1 (5.3)	1 (8.3)
Interventions			
Muscle strengthening exercises (MSE)	23 (74.2)	13 (68.4)	10 (83.3)
Aerobic endurance training (AET)	21 (67.7)	12 (63.2)	9 (75.0)
Home exercise program (HEP)	21 (67.7)	11 (57.9)	10 (83.3)
Massage therapy and mobilization therapy (MT)	14 (45.2)	10 (52.6)	4 (33.3)
Exercises targeting activities in daily living (ADL)	11 (35.5)	3 (15.8)	8 (66.6)
Respiratory care (RC)	2 (6.4)	1 (5.3)	1 (8.3)
Other	2 (6.4)	1 (5.3)	1 (8.3)

AL: activity level; BL: body level; STS: sit to stand movement. More than one option could be stated so percentages add up to more than 100%.

REFERRAL AND TREATMENT PATTERNS

Of the 20 patients who were referred because of muscle weakness, 16 (80%) had muscle strength improvement as a treatment objective and 14 (70%) received MSE. Thirteen patients were referred for improving general condition, whereas nine (69%) had this as a treatment goal and eight (62%) received AET for improving the general condition. Overall we saw a discrepancy between referral reason and objective in 32% of cases, while in 47% the referral reason and intervention were not aligned (Fig. 1).

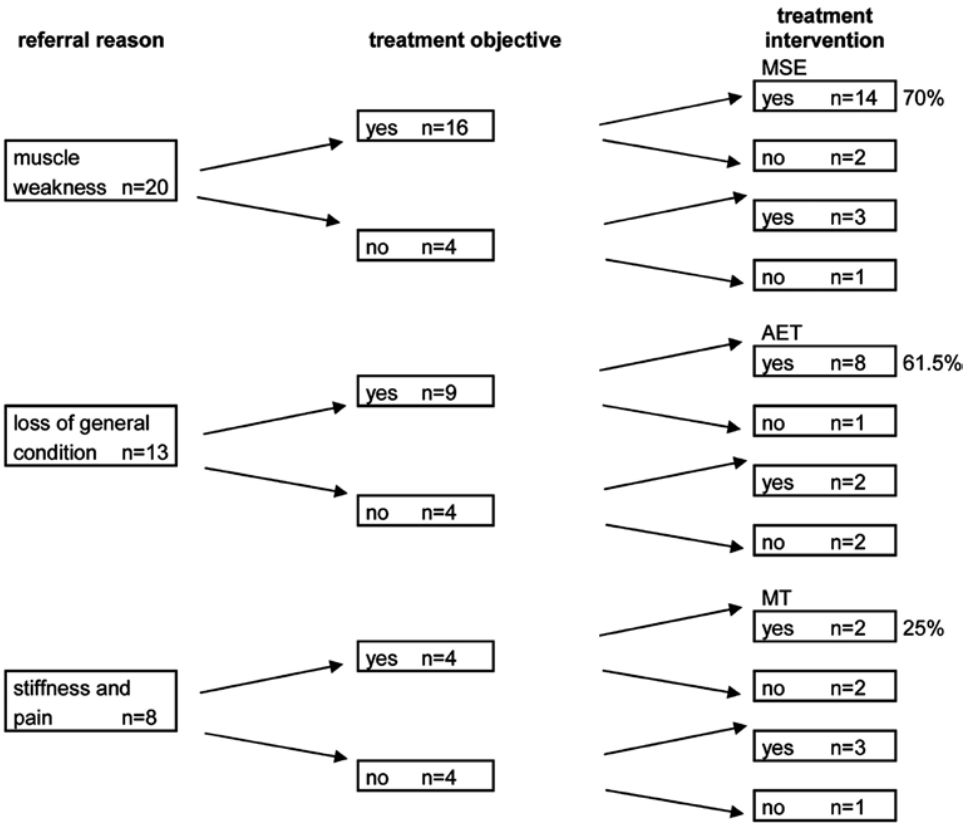

Fig. 1 | Referral and treatment patterns reported by 31 therapists.

MSE: muscle strengthening exercises, AET: aerobic exercise therapy, MT: massage/mobilization techniques. For reason for referral that is more than N= 5.

EFFECT OF TREATMENT AND NEED FOR GUIDELINES

All patients (n = 52) who ever received physiotherapy were asked if, in their opinion, physiotherapy resulted in the desired effect. One patient could not indicate this because therapy had just started. Overall, 60% of patients responded

positively to this question (66% of mildly affected and 46% of more severely affected patients, $p > 0.1$).

Patients receiving physiotherapy at the time of this study more often perceived the intervention to have the desired effect than those who stopped (72% versus 30%, $p = 0.01$). Eleven of the 20 patients who had stopped did so because of a lack of effect or negative side-effects such as extreme fatigue, muscle pain or bursitis; five (25%) because their rehabilitation program ended after 3 months and continuation was not covered by their insurance company; four (20%) had reached their treatment goal.

All 31 therapists were asked if the (intermediate) treatment objectives were reached. Nine therapists could not indicate this due to a short treatment period (less than 4 weeks). Of the 22 remaining therapists 14 (64%) indicated that objectives were reached; two stated that treatment goals were partially reached and six stated that they were not reached. Different outcome measures were used.

Due to the multiple intervention combinations it was not possible to evaluate which intervention (or combination) was perceived as most effective. The percentages of patients and therapists reporting an effect for MSE, AET, HEP, MT and ADL were similar (between 55 and 75%). All therapists except one (97%) and 73% of patients indicated that there is a need for guidelines for the physiotherapy treatment of Pompe patients.

DISCUSSION

This survey shows that physiotherapeutic care of Pompe patients in the Netherlands consists of a wide range of treatment interventions. About 60% of the patients were ever referred to the physiotherapist, with more severely affected patients being referred more often. Referral reasons varied, and were not always in line with the interventions used. The most commonly used intervention was muscle strengthening exercises (MSE), often in combination with aerobic exercise therapy (AET). More than half of the patients and therapists perceived physiotherapy as beneficial and the majority highlighted the need for guidelines.

The observed variation in referral reasons and interventions can partly be explained by the wide spectrum of symptoms and needs of Pompe patients [9]. Nevertheless, the referral pattern was not always consistent with the clinical picture of Pompe disease. It is unclear, for example, why half the patients who were independent on walking aids were referred to a physiotherapist, while the other half were not. In addition, at the moment of this study, less than 40% of the Dutch Pompe patients were treated by a physiotherapist. Both observations may indicate that there is confusion about the treatment opportunities and their use. Both clinicians and patients highlighted the need for guidance, supporting this notion.

The applied intervention could also not always be explained by the clinical picture. We observed a discrepancy between the referral reasons, treatment objectives and the actual interventions. Only 53% of the treatment interventions and 68% of the objectives were in line with the referral reasons. In addition, frequency, and duration of interventions varied substantially between patients. Physiotherapists have little chance to develop relevant experience with this rare disease, and will

likely see only one or two Pompe patients during their career, which may explain the wide range of interventions and treatment objectives. Personal preference and the lack of research evaluating the effectiveness of physiotherapy in the management of Pompe disease may further contribute to the wide range of interventions and discrepancy.

A number of studies, mostly hampered by small numbers of patients, have investigated the effect of physiotherapy in Pompe disease [10-14]. Three studies reporting on the effect of aerobic exercises—either combined with strengthening exercises or a high-protein diet—showed either improvement or stabilization in muscle strength [10-12]. In two studies respiratory muscle training was described to increase respiratory muscle strength [13, 14]. Due to the small numbers of patients and the diverse interventions and outcome measures used, firm conclusions about the effectiveness of these interventions cannot be drawn. Therefore, there is a clear need for further studies on the effectiveness of physiotherapy for Pompe patients.

This is the first study to describe the present physiotherapeutic practice for patients with Pompe disease. A limitation of this study was its subjective and retrospective character, which might have influenced the reliability of the data. More than half of the patients and almost two-thirds of physiotherapists perceived physiotherapy as beneficial. Although patients reported a benefit from treatment, it was not possible to assess how this corresponded with changes in outcomes such as an increase in muscle strength or the ability to do more activities in daily living. Moreover, the opinions of therapists were based on different outcome measures so the results of their treatment were not mutually comparable. Therefore, this study does not allow any statements on the effectiveness of interventions or about which intervention (combination) fits Pompe patients best. We were also not able to compare the perceived benefit of

physiotherapy between patients receiving and not receiving ERT due to the small number of patients not receiving ERT and differences in disease severity between these patient groups. Finally, not all therapists were traceable, reducing the number of observations for certain variables.

Some suggestions can be made however. The observation that mildly affected patients reported more benefit than moderate to severely affected patients suggests that this group might benefit more from physiotherapy. The most commonly used intervention was MSE (74%), and the combination with AET was the most frequently applied. Future studies on the effectiveness of physiotherapy should have a prospective design with a core set of outcome measures. They should focus firstly on the effectiveness of the most frequently observed interventions such as AET combined with MSE as an addition to ERT in Pompe patients of different disease severity. Further, the development of a physiotherapy network consisting of an expert centre and a selected group of physiotherapists who see several Pompe patients would ensure that therapists are more familiar with the disease as well as form a platform for further studies.

CONCLUSIONS

Physiotherapeutic care of Pompe patients in the Netherlands is perceived as beneficial although it is scattered and diverse. The variety in interventions can only partly be explained by the heterogeneity of symptoms. Care of patients may be sub-optimal and improvements can be made by tailoring interventions to the referral reasons and treatment objectives.

The rarity of the disease and the lack of scientific evidence and guidelines hamper further optimization of treatment. However, due to the wide clinical spectrum of the disease it is difficult to make a uniform treatment program. Therefore, clinical trials are urgently needed, exploring the type and content of interventions that are most beneficial to Pompe patients in different stages of disease severity.

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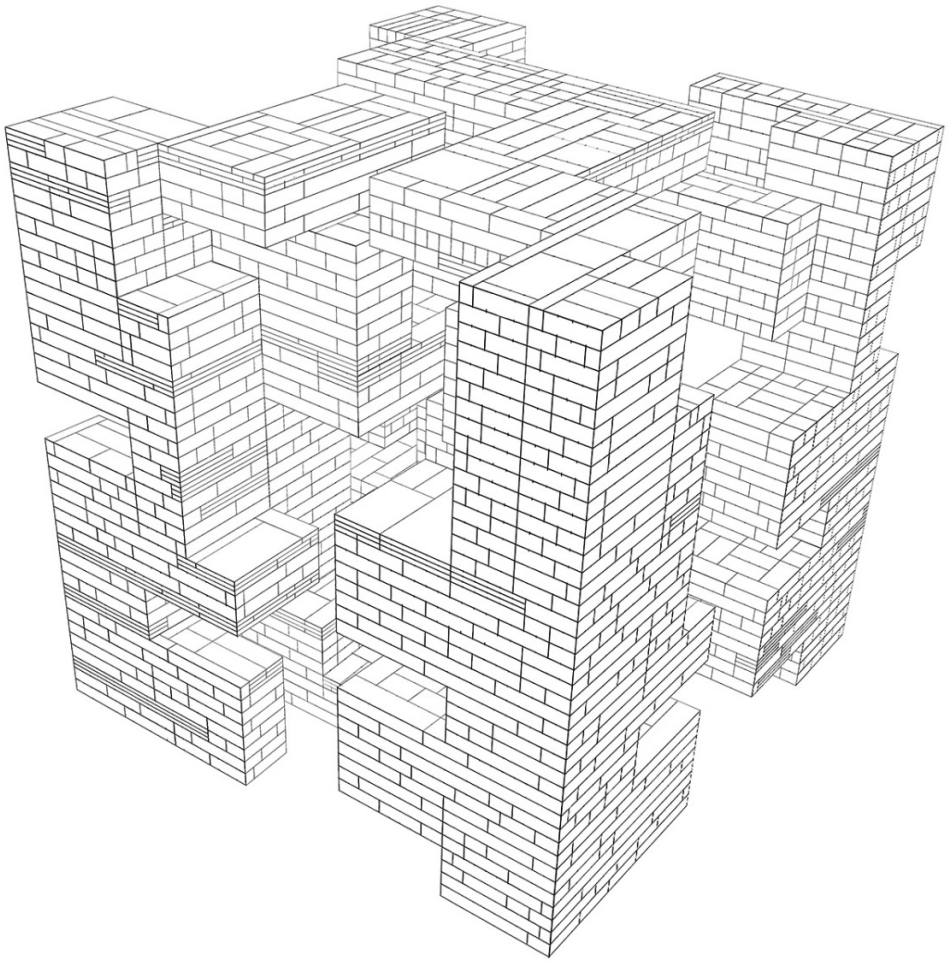

CHAPTER 03

SAFETY AND EFFICACY OF EXERCISE TRAINING IN ADULTS WITH POMPE DISEASE:

EVALUATION OF ENDURANCE, MUSCLE STRENGTH AND CORE STABILITY BEFORE AND AFTER A 12 WEEK TRAINING PROGRAM

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ABSTRACT

BACKGROUND

Pompe disease is a proximal myopathy. We investigated whether exercise training is a safe and useful adjuvant therapy for adult Pompe patients, receiving enzyme replacement therapy.

METHODS

Training comprised 36 sessions of standardized aerobic, resistance and core stability exercises over 12 weeks. Before and after, the primary outcome measures safety, endurance (aerobic exercise capacity and distance walked on the 6 min walk test) and muscle strength, and secondary outcome measures core stability, muscle function and body composition, were evaluated.

RESULTS

Of 25 patients enrolled, 23 successfully completed the training. Improvements in endurance were shown by increases in maximum workload capacity (110 W before to 122 W after training, [95 % CI of the difference 6 · 0 to 19 · 7]), maximal oxygen uptake capacity (69 · 4 % and 75 · 9 % of normal, [2 · 5 to 10 · 4]), and maximum walking distance (6 min walk test: 492 meters and 508, [−4 · 4 to 27 · 7]). There were increases in muscle strength of the hip flexors (156 · 4 N to 180 · 7 N [1 · 6 to 13 · 6) and shoulder abductors (143 · 1 N to 150 · 7 N [13 · 2 to 35 · 2]). As an important finding in secondary outcome measures the number of patients who were able to perform the core stability exercises rose, as did the core stability balancing time ($p < 0.05$, for all four exercises). Functional tests showed small

reductions in the time needed to climb four steps (2 · 4 sec to 2 · 1, [− 0 · 54 to −0 · 04]) and rise to standing position (5 · 8 sec to 4 · 8, [−2 · 0 to 0 · 0]), while time to run, the quick motor function test results and body composition remained unchanged.

CONCLUSIONS

Our study shows that a combination of aerobic, strength and core stability exercises is feasible, safe and beneficial to adults with Pompe disease.

BACKGROUND

Pompe disease (glycogen storage disease type II, acid maltase deficiency) (OMIM # 232300) is a rare metabolic myopathy caused by glycogen accumulation resulting from deficiency of lysosomal acid α-glucosidase (GAA). It presents as a wide clinical spectrum, the most prominent symptoms in adults being proximal skeletal muscle weakness and respiratory problems [1, 2]. Skeletal muscle weakness typically fits a pattern of limb-girdle myopathy, with the abdominal and paraspinal muscles and the musculature of the hip being the most affected muscle groups [3-5].

Enzyme replacement therapy (ERT) with recombinant human acid α-glucosidase (Myozyme/Lumizyme) was approved for the treatment of Pompe disease in 2006. In adults, ERT has been shown to elicit positive effects on skeletal muscle strength, walking distance, respiratory function and survival [6-8]. Patients' fitness and physical functioning may be further supported by treatments additional to ERT, such as exercise training. Although some recent studies suggest that exercise training may be beneficial, evidence is still limited [9, 10].

A recent study on common clinical practice in the Netherlands showed that there is a lack of uniformity in the type of physical therapy training programs applied, and that physical therapists and patients all seek guidance and standardization [11]. We therefore aimed to determine whether a standardized and well-structured exercise intervention program combining aerobic, resistance and core stability exercises was feasible and safe, and whether it added value to treatment with ERT alone. In a group of relatively mildly affected adult Pompe patients receiving ERT for more than a year, we evaluated the effects of such a regime on endurance, muscle strength and function, core stability, and body composition.

METHODS

PATIENTS

Patients were recruited at the Centre for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Centre, Rotterdam, the Dutch national referral centre for patients with Pompe disease.

There were three inclusion criteria:

1. A confirmed diagnosis of Pompe disease measured by decreased acid α-glucosidase activity in leukocytes or fibroblasts, and mutation analysis;
2. Age > 17 years;
3. Treatment with ERT for at least 52 weeks

There were four exclusion criteria:

1. The use of walking-aids or a wheelchair;
2. Ventilator-dependency;
3. Concurrent medical conditions;
4. Participation in other exercise-training programs.

The study was approved by the Ethical Committee at Erasmus MC University Medical Centre. Informed consent was obtained from all patients.

STUDY DESIGN AND INTERVENTION

Three times a week for 12 weeks, all patients followed a standardized training program that was provided under the supervision of physical therapists at carefully selected sports or fitness centres near the patients' homes. To ensure the uniformity of the program and its supervision, all therapists attended a one-day instruction program at Erasmus MC University Medical Centre. The training program is depicted in Fig. 1. The first training session was on-site supervised by one of the researchers from Erasmus MC (LvdB, MF), who subsequently attended each training site every two weeks to monitor proper conduct of the program.

Patients were randomly subdivided into two groups: group 1 (n = 13), which started the training program at week 1; and group 2 (n = 12), which started at week 13. The staggered start of training allowed us to investigate whether any improvement observed in the training period could also be attributed to ERT. Furthermore, the duration of the effect of the training program can be evaluated from the follow-up of patients in group 1 after they stop training in week 12.

To assess the effects of the program, each patient visited our centre (Erasmus MC) on two separate days in weeks 0, 12 and 24. The primary endpoints of this study were safety, endurance and muscle strength. Secondary endpoints were core stability, muscle function, and body composition.

Under the supervision of the physical therapist, training diaries were kept by all patients, who recorded the days on which they trained, the weight and number of repeats of resistance exercises, and the perceived level of exertion. To evaluate training progress and patients' motivation, patients were telephoned weekly.

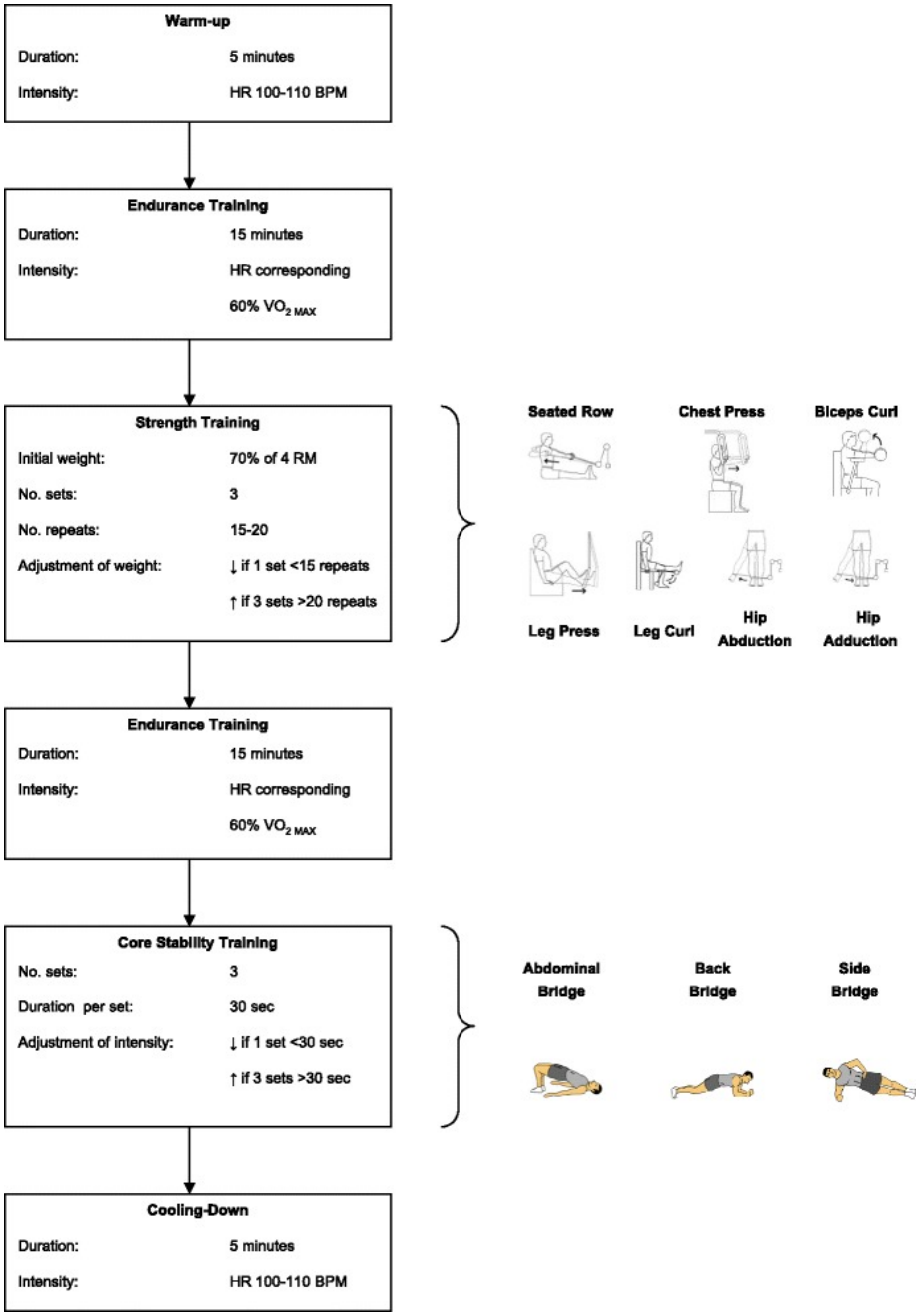

Figure 1 | Flowchart for the standardized exercise-training regime combining aerobic, resistance and core stability exercises

ASSESSMENTS

SAFETY

Plasma CK was measured every two weeks as a safety marker for exercise-induced muscle damage [12], and patients were contacted every week to record potential side effects such as pain and fatigue.

ENDURANCE

Aerobic (endurance) exercise capacity was determined using an incremental cycle ergometer. After 4 min of unloaded cycling on the cyclo ergometer (Jaeger ER 800; Erich Jaeger, Würzburg Germany) exercise intensity was increased progressively until exhaustion (i.e. ramp protocol), during continuous measurement of patients' heart rates and ventilator parameters using spiro ergometry equipment (Oxycon Pro, Jaeger, Würzburg, Germany). The rate of increase was determined considering the patient's functional capacities and ranged from 5–20 Watts/minute. The duration of every individual test exceeded 6 min but did not take longer than 12 min. At exhaustion, the rating of exertional symptoms was assessed using the Borg scale (scale 6–20) [13], patients consistently scoring 14 or above. Maximum workload capacity (WMAX) and, peak oxygen uptake capacity (VO2 PEAK) were measured. The ventilatory threshold (VT) was assessed independently by two clinical exercise physiologists using the ventilatory equivalents method [14]. The test was considered to be maximal when one of the following criteria was met [14]:

1. heart rate > 90 % of that predicted,
2. respiratory exchange ratio (RER) > 1 · 11, or
3. VO2 stabilized despite increased workload.

Walking distance on the 6-min walk test (6MWT) was evaluated according to the American Thoracic Society guidelines.

Core Stability

To assess the dynamic balance, which reflects core stability, one physical therapist (MF) measured time in balance (in seconds) for each of the four core stability exercises of the training program (Fig. 1) [15].

Muscle strength

Muscle strength was assessed by one investigator (SW) using Hand-held Dynamometry (HHD). Assessments were performed in a standardized manner, and sum scores were calculated as described previously [6].

Muscle Function

Functional activity assessments comprised three timed tests: 10 meter running, climbing four steps, and rising from supine to standing positions [16], and the Quick Motor Function Test (QMFT), a test specifically designed and validated for Pompe patients [17]. The QMFT consists of 16 specific motor skills related to daily activities. A total score is achieved by summing the scores for each item (ranging from 0 “cannot perform” to 4 “can perform with no effort”), and is expressed as a percentage of the maximum score.

Body composition

Bone-mineral density (BMD) and body-composition measurements were performed conform DXA technology using a Lunar DPX densitometer and analysed with Encore 2002 software (GE Lunar DPX, GE Health Care). Bone densitometry was performed in a standardized manner as described previously

[18]. Body composition was described in terms of the mineral, lean and fat body mass (kilograms). The percentage of fat mass and, more specifically, android and gynoid fat, were calculated.

STATISTICAL ANALYSIS

Patient characteristics were summarized using descriptive statistics. Data for the two groups were combined after verifying that there were no significant differences between outcome measures before the start of the training (group 1 – week 0; group 2 – week 12; student's t-test for normally distributed, and Mann–Whitney for not-normally distributed data).

Mean differences before and after the training were compared using the paired t-test for normally distributed data, and otherwise the Wilcoxon signed rank test for paired samples. For group 2, we also used these tests to compare the outcome measures before and after 12 weeks of ERT only (week 0 to 12).

Significance level was set at $p < 0 \cdot 05$. Statistical analyses were performed using SPSS for Windows (release 17 · 0; SPSS, Inc., Chicago, IL).

RESULTS

PATIENTS

A total of 25 patients fulfilled the inclusion criteria and chose to participate in this study. Two patients did not complete the training program because they were insufficiently motivated. This left 23 patients, who successfully completed the study. Their ages ranged from 20 to 71 years (median of 46 years). They had been receiving ERT for 1 to 6 years with a median of 3 years (Table 1).

Table 1 | Patient characteristics

	Group 1 (n=12)	Group 2 (n=11)	Total group (n=23)	P-value *
Male gender (%)	7 (58%)	5 (45%)	12 (52%)	0.54
Age in years (range)	45.4 (19.6-70.5))	46.6 (32.9-66.1)	46.0 (19.6-70.5)	0.85
Disease duration in years (range)	15.5 (8.1-28.1)	16.1 (6.0-32.1)	15.8 (6.0-32.1)	0.83
ERT duration in years (range)	3.3 (1.4-6.5)	3.0 (1.3-3.6)	3.1 (1.3-6.5)	0.96
Training sessions (max. 36)	33 (27-36)	32 (24-35)	32 (24-36)	0.70

Group 1 trained in weeks 1–12 and Group 2 trained in weeks 13–24
ERT enzyme replacement therapy
* For the difference between group 1 and 2 (chi-2 test for proportions and Wilcoxon signed rank test for continuous data)

Effect of ERT only

During the 12 weeks before training started, patients in group 2 (ERT only) underwent the same set of assessments as in the 12 weeks of training (ERT plus training). This enabled us to use group 2 to compare the effects of ERT only with the combined effects of ERT and training. During the first 12 weeks of ERT only, we detected no significant improvements in the main outcome measures.

Effect of training

Patients in the two randomly assigned groups were comparable in terms of age, gender, disease duration, time on ERT, number of training sessions completed, and baseline test results. This allowed us to analyse the effect of training in the total group of 23 patients.

SAFETY

During the first week of training, two patients had a high plasma CK level (10125 U/l and 6149 U/l), and also experienced muscle pain and fatigue. Over the following week, their CK-values dropped to their normal range, and the fatigue and pain disappeared. Both patients continued training. None of the other patients had pain, fatigue, or increases in plasma CK levels during the study period.

ENDURANCE

All patients were able to complete the incremental cycle test without adverse events. One was excluded from the analysis because he did not reach the required maximum intensity defined in the method section. After 12 weeks of training WMAX, VO2peak and VT improved significantly (Table 2). VO2peak and VT increased both in absolute values and adjusted for body weight or as a percentage of normal values. The ratio VT/VO2peak did not change, as both the numerator and the denominator increased. There were no significant differences between patients' maximum heart rates before and after 12 weeks of training, indicating that the results were truly based on an increase in fitness rather than on greater exertions by the patients towards the end of the training period. FVC did not change. Average walking distance on the 6MWT increased by 16 meters ([4.4-27.7], $p = 0.01$).

Table 2 | Aerobic fitness measured in an incremental cycle test and a 6-min walk test before and after 12 weeks of training

	Before training Mean ± SD	After training Mean ± SD	P-value *
Incremental cycle test (N = 22a)			
Ventilatory threshold (VT)			
- Absolute values (l/min)	1.25 ± 0.36	1.38 ± 0.36	<0.01
- Adjusted for body weight (ml/min/kg))	16.7 ± 4.3	18.5 ± 4.7	<0.01
- VT/VO_2 peak (%)	77.6 ± 12.1	78.3 ± 12.3	0.742
Data at exhaustion			
- Maximum workload (Wmax, Watt)	110 ± 52	122 ± 53	<0.01
- Maximum heart rate (bpm)	156 ± 25	161 ±20	0.16
- Pulmonary ventilation (l/min)	59.6 ± 20.2	68.2 ± 21.0	<0.01
- Tidal volume (l)	1.85 ± 0.48	1.85 ± 0.44	0.91
- Gas exchange ratio	1.15 ± 0.09	1.14 ± 0.08	0.71
Peak oxygen uptake (VO_2 peak)			
- Absolute values (l/min)	1.67 ± 0.62	1.82 ± 0.60	<0.01
- Adjusted for body weight (ml/min/kg)	22.1 ± 7.0	24.1 ± 7.1	<0.01
- As % of normal	69.4 ± 17.4	75.9 ± 18.0	<0.01
6 min walk test (N=22)			
- Maximum walking distance (6MWT, m)	492 ± 89	508 ± 97	0.01
Pulmonary function test (N=23)			
- Forced vital capacity (FVC, % of normal)	89.2 ± 12.6	90.0 ± 14.0	0.51

* For the difference before and after training (paired samples t-test)

[a] One patient was excluded because he did not reach the required maximum intensity

CORE STABILITY

Figure 2 shows the results of the core stability tests. At the start of the program, many patients experienced difficulties in performing the core stability exercises, reporting problems with initiating movement and controlling balance. During the training program, the number of patients who were able to perform the exercises increased for three of the four exercises (from 17 to 21 for the abdominal bridge, 15 to 16 for the left side bridge and 13 to 16 for the right side bridge). The average time they were able to remain in balance improved for all four positions (by 58 % for the back bridge, 229 % for the left and 223 % for the right side bridges, and 86 % for the abdominal bridge; $p < 0 \cdot 05$).

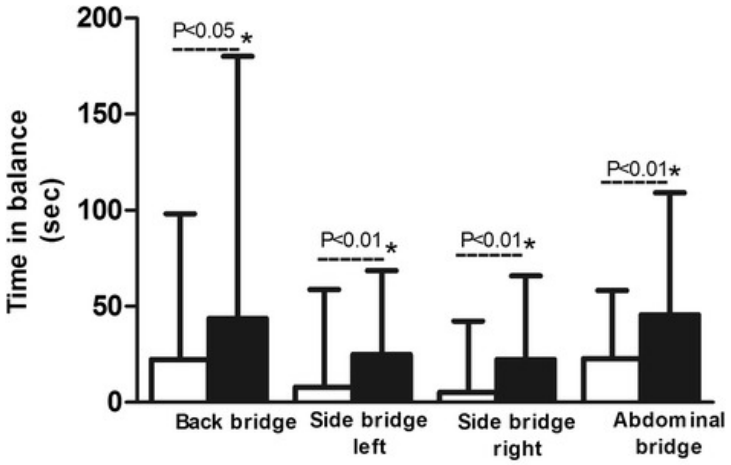

Figure 2 | Time patients (N = 23) were able to remain in balance for the four different core stability exercises before (white bars) and after training (black bars)

MUSCLE STRENGTH

Of the nine muscle groups tested, there were increases in the strength of the hip flexors and shoulder abductors (Table 3).

Table 3 | Muscle strength measured by hand-held dynamometry (HHD) before and after 12 weeks of training

HHD of individual muscle groups in Newton (N=23)	Before training Mean ± SD	After training Mean ± SD	P-value *
Neck extensors	142.1 ± 18.4	140.4 ± 13.8	0.65
Neck flexors	124.7 ± 40.2	132.1 ± 33.9	0.09
Shoulder abductors	143.1 ± 29.1	150.7 ± 35.4	0.02
Elbow flexors	226.4 ± 41.5	230.8 ± 42.3	0.42
Elbow extensors	180.5 ± 20.1	176.2± 25.3	0.27
Hip flexors	156.4 ± 61.9	180.7 ± 57.7	< 0.01
Hip abductors	159.4 ± 58.3	158.0 ± 68.1	0.75
Knee extensors	189.2 ± 34.1	193.0 ± 31.8	0.27
Knee flexors	121.2 ± 56.2	122.6 ± 56.7	0.51

*For the difference before and after training (paired samples t-test

MUSCLE FUNCTION

Twelve weeks of training significantly reduced the time taken by patients to climb four steps (on average 0.3 sec less, [−0 · 54 to −0 · 04], p = 0.02 Table 4) and to rise from supine to a standing position (1 sec less, [−2.0 to 0 · 01], p = 0.05). The QMFT sum score and the time to run 10 meters did not change.

Table 4 | Muscle function measured by the quantitative motor function test (QMFT) and timed tests before and after 12 weeks of training

	Before training Mean ± SD	After training Mean ± SD	P-value *
QMFT score (N = 22[b])	51 ± 8	51 ± 9	0.65
Timed Test (N = 22[b])			
- **10 m running (sec)[a]**	4.97 ± 1.50	4.70 ± 1.34	0.13
- **Climbing four steps (sec)[a]**	2.37 ± 0.80	2.08 ± 0.74	0.02
- **Rising from supine to standing position (sec)[a]**	5.83 ± 4.25		0.05

* For the difference before and after training (paired samples t-test and the Wilcoxon signed-ranks test for paired data [a])

[b] QMFT score and timed test were not available for one patient

BODY COMPOSITION

There were no changes in mineral bone mass (2 · 83 kg ± 0 · 58 before training vs. 2 · 82 kg ± 0 · 57 after training), in lean body mass (42 · 53 kg ± 7 · 99 vs. 43 · 14 kg ± 8 · 28), or in fat mass (30 · 11 kg ± 9.23 vs. 29 · 29 kg ± 9 · 06). Likewise, there were no changes in bone mineral density, overall fat percentage, and android and gynoid fat percentages (results not shown).

DURATION OF TRAINING EFFECT

After the initial 12 weeks of training group 1 was planned to discontinue training, but 11 of 13 patients chose to continue training with the same or slightly modified intensity. Therefore we were not able to assess how long the training effect maintained after withdrawal.

DISCUSSION

This study provides clinical evidence that a combination of aerobic, resistance and core stability training can be performed safely in patients with Pompe disease, and helps to improve endurance, core stability and muscle function.

Improved endurance was shown by improved aerobic fitness over 12 weeks of training. In addition to the 11 % increase in maximum workload capacity, peak oxygen uptake and ventilatory threshold improved by 9 % and 10 %, and the 6MWT by 3 %. The increase in peak oxygen uptake was relatively small compared to a number of studies in neuromuscular dystrophies and metabolic myopathies like McArdle disease, showing an increase ranging from 12-47 % [19-22]. In these studies, patients spent more time per week on endurance training, which might explain the larger increase. A second explanation might be the lower baseline VO2peak than in our study.

The baseline values on VO2peak we found in our study were slightly higher than those reported in two Italian studies of Pompe patients (range 15.1 – 26.4 ml/kg/min) [23, 24]. These include 8 patients who were assessed prior to treatment (median 20.5 mg/kg/min), and one patient assessed during ERT (15.7 mg/kg/min), while all our patients had been on ERT for at least a year, which might explain the somewhat higher VO2peak values in our cohort. Nevertheless, our 6MWT results also suggest that our cohort had a relatively good endurance capacity before the training (77 % of normal expected). Finally, their ventilatory threshold as a percentage of the peak oxygen uptake (78 %) is relatively high for an untrained population, and comparable to that seen in the three Italian patients that reached the VT (five did not reach the VT in this study, while all our patients reached VT). Our patients thus had relatively good endurance and tolerance

capacity before training, which is in agreement with the fact that mildly affected Pompe patients were selected for this study.

So far the 6MWT was used in clinical trials for Pompe disease to assess endurance capacity, but since most patients have walking difficulties it has been questioned whether the 6MWT fully reflects this [25, 26]. Our study indicates that the incremental cycle test offers a good alternative to test endurance capacity, providing insight into patients' aerobic capacity.

Core stability has not been trained previously in neuromuscular disorders presenting with limb-girdle weakness. One possible reason may lie in the assumption that core stability exercises are not feasible for such patients. Indeed, on starting training, many patients had difficulty performing the exercises. During the program, however, they learned to activate the proper muscle groups and were able to remain in balance for longer. Our results thus indicate that core stability training is feasible and improves time in balance in patients with Pompe disease who are treated with ERT. Feedback from patients during the training also suggests that they perceived their improved core stability to facilitate daily activities. Further studies on how training influences patient reported outcomes such as quality of life are needed.

An increase in muscle strength was observed in two of the nine muscle groups tested: the hip flexors and shoulder abductors. We are not completely certain whether the increased strength of the hip flexors resulted from strength training, core stability exercises, or both. Core stability may support gains in muscle strength by improving proprioception and coordination.

The combined effects of the training program on endurance, core stability, and muscle strength also led to some functional improvement, with patients becoming able to climb four stairs and rise to a standing position faster.

In our study all patients received enzyme replacement therapy. It has been reported that the main incremental effects of enzyme replacement therapy (ERT) are observed during the first year. Therefore only patients who had received ERT more than 1 year were allowed to participate. The study had a staggered design with patients in group 2 starting after a period of no training allowing evaluation of the effect of ERT only, and patients in group 1 scheduled to stop training after 12 weeks with the intention to study how long the effect of training continued. During ERT only patients remained more or less stable indicating that training was the main driver behind the effects. We were not able to assess how long the training effect continued, since all patients in group 1, except two, chose to continue training after 12 weeks. Although patients' choice interfered with our study design, it also reflects the positive feedback they have given us on the program.

Compliance was high in our study. It is likely that the beneficial effects experienced, the supervision by physiotherapists and weekly telephone consultations contributed to this. We therefore recommend that the program be incorporated into regular supervised physiotherapy sessions.

Few studies have been conducted on exercise and training in Pompe disease. The largest so far was performed before ERT became available [9]. For a mean duration of four years, 26 patients participated in a combined nutrition and endurance exercise therapy program that led to improved muscle function as measured with the Walton score. More recently, a German observational study showed that the effect of ERT on walking distance was most pronounced in five patients who, incidentally, were also subjected to endurance training on a cycle ergometer during ERT infusions [10]. Two other studies, one in mice and one in five adult patients with Pompe disease, however, did not confirm a beneficial effect of endurance training while receiving ERT [27, 28].

Previous exercise studies in Pompe disease mainly focused on endurance training. It has been envisaged that resistance training might lead to muscle damage, thereby aggravating muscle weakness [29-31]. Prior to our study, only Terzis et al. [28] combined endurance with resistance training in five patients with Pompe disease receiving ERT. The combined results of these five patients showed that both muscular strength and walking distance improved.

Before starting our study we carefully considered whether we should perform exercise-endurance training only, or a combination of different types of exercises. We chose the latter, because we not only wanted to improve endurance, but also target all affected muscles (resistance exercises), and ameliorate proprioception and the strength of those proximal muscles not targeted by resistance training (core stability exercises). Our decision to use a combined program was also driven by the fact that our patient population was not large enough to run three separate programs.

Although we cannot rule out the possibility that endurance training alone might have had a greater impact on endurance, we observed that the extra exercises had positive effects on core stability, and may also have improved muscle strength and function. Earlier studies in patients with inherited muscular myopathies did not include core stability exercises; our study shows them to be both safe and easy to learn. Patients in our study were mildly affected; those who are more severely affected may need slightly adjusted exercise-training programs but we recommend to include similar components.

CONCLUSIONS

Our study shows that a combination of endurance, strength and core stability training is feasible and can be performed safely in patients with Pompe disease. Such training helps to improve endurance, muscle strength, muscle function and core stability. This training program thus seems to offer added value for Pompe patients to those of ERT.

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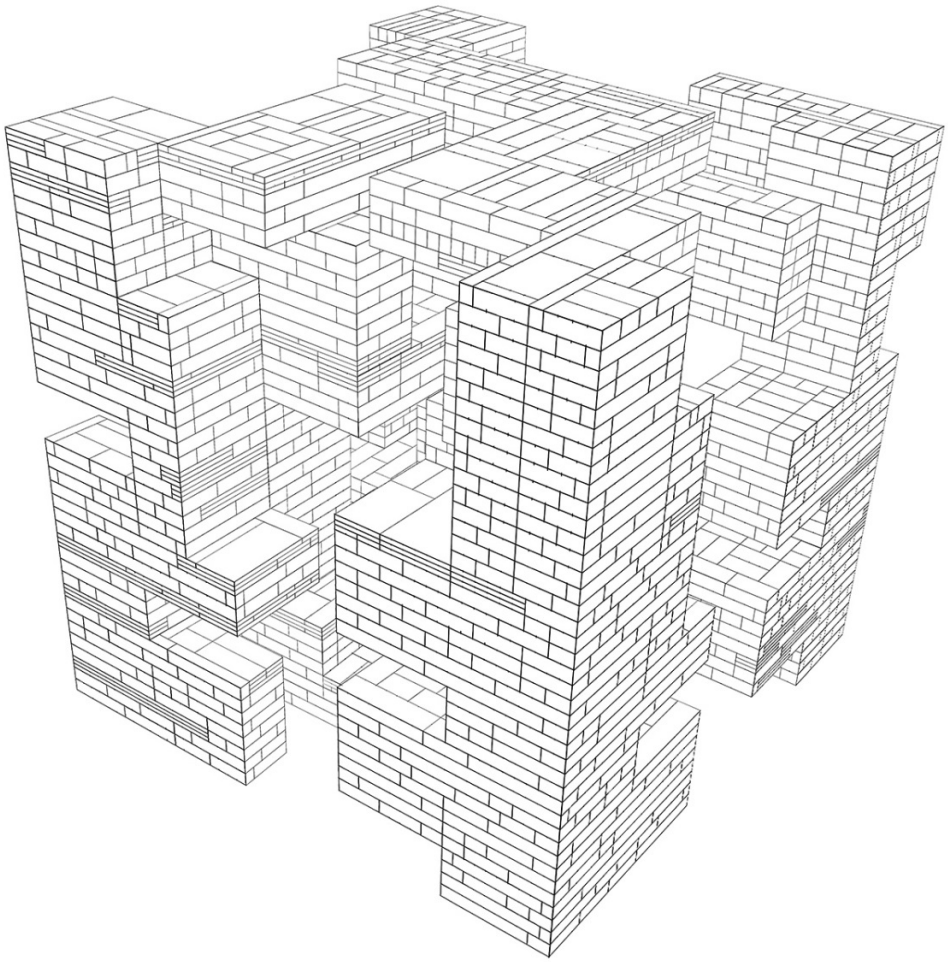

CHAPTER 04

EXERCISE TRAINING IN ADULTS WITH POMPE DISEASE:

THE EFFECTS ON PAIN, FATIGUE, AND FUNCTIONING

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ABSTRACT

OBJECTIVE

To assess if a 12-week exercise intervention to improve aerobic fitness, muscle strength, and core stability also had an impact on fatigue, pain, activity, and participation in adults with Pompe disease, an inherited neuromuscular disorder.

DESIGN

Open-label trial. Change was assessed by the chi-square test and Wilcoxon signed-rank test.

SETTING

Physiotherapy practices.

PARTICIPANTS

Mildly affected adult patients with Pompe disease who were not dependent on ventilators and/or walking devices and were receiving enzyme replacement therapy.

INTERVENTION

Patients participated in a 12-week exercise program, which included 36 sessions of standardized aerobic, resistance, and core stability exercises.

MAIN OUTCOME MEASURES

Before and after the training program we evaluated fatigue (Fatigue Severity Scale), pain (yes/no), motor function (Quantitative Muscle Function Test, Rasch-

built Pompe-specific Activity Scale), amount of physical activity (activity monitor), and health status (Medical Outcomes Study 36-Item Short-Form Health Survey).

RESULTS

Of the 25 patients enrolled, 23 completed the program. At the end of the program, levels of fatigue (median, 5.33 to 4.78, *P*=.01) and pain (56.5% to 21.7%, *P*=.04) improved. The quality of motor function and the amount of physical activity patients engaged in did not change. Changes in pain and fatigue were not related to improvements in aerobic fitness or muscle strength.

CONCLUSIONS

This study in mildly affected adult patients with Pompe disease suggests that a combined training program aiming to increase aerobic fitness, muscle strength, and core stability also leads to improvements in fatigue and pain.

Pompe disease is an inheritable neuromuscular disease caused by a deficiency of the lysosomal enzyme acid alpha-glucosidase, which results in a glycogen accumulation in cells. The disease has a broad clinical spectrum; in adult patients it primarily affects skeletal and respiratory muscles [1].

In 2006, enzyme replacement therapy (ERT) with recombinant human acid alpha-glucosidase became available. ERT has been shown to improve skeletal muscle strength, walking distance, respiratory function, and survival in adult patients [2-5]. The most prominent effects were obtained in the first year of ERT and stabilized thereafter [3].

Complementary therapies such as exercise therapy may further enhance patients' functioning and quality of life. A few studies have demonstrated a positive effect of exercise therapy in Pompe disease [4, 6-8]; no study has reported negative effects. However, insufficient conclusions can be drawn from these studies because of the combination of exercise training with other adjuvant therapies and/or the small number of patients included. Our recently reported controlled training study further strengthens the evidence for a beneficial effect of exercise training [9].

In this recent study, 23 mildly affected patients with Pompe disease receiving ERT completed a training program consisting of a combination of aerobic, resistance, and core stability exercises [9]. The first report on this study focused on the outcomes directly related to the intervention and showed that this training regimen resulted in significant improvements in aerobic fitness, muscle strength, core stability, and distance walked. These outcome measures mostly represent functioning at the body function and structure level as described in the International Classification of Functioning, Disability and Health (ICF)[10]. This report did not cover the activity and participation levels of this classification (ie,

functioning of a person as a whole and functioning in a social context), which are also key to the assessment of functioning. Pompe disease strongly affects patients' ability to carry out daily life activities and participation and is furthermore associated with fatigue and pain, suggesting that these are indeed important parameters to take into account in the evaluation of treatment for this disease [11-13].

Therefore, the aim of this study is to present the effect of the combined training program on pain, fatigue, activity, and participation. To gain insight into the extent to which functional measures were related to the direct training goals, we also studied the correlations between the different domains of the ICF model.

METHODS

PARTICIPANTS

As described in our recent report [9], patients were recruited at the Center for Lysosomal and Metabolic Diseases, Erasmus MC University Medical Center, Rotterdam, The Netherlands, which is the national referral centre for patients with Pompe disease. The study was approved by the Ethical Committee of the Erasmus MC University Medical Center. Inclusion criteria were a confirmed diagnosis of Pompe disease, age >17 years, receiving ERT for at least 1 year, and not dependent on a ventilator and/or walking device. Concurrent relevant medical conditions (eg, cancer, cardiovascular diseases) and participation in other exercise training programs were exclusion criteria. From January to September 2010, 105 adult patients with a confirmed diagnosis of Pompe disease were seen in our centre. A neurologist (S.C.A.W.) checked the patients for our inclusion and exclusion criteria. Twenty-five patients fulfilled the criteria and were asked to participate in the study. All patients agreed and signed informed consent.

INTERVENTION

All patients were trained under supervision of physiotherapists at carefully selected outpatient clinics. To ensure the uniformity of the training program and its supervision, all therapists attended a 1-day instruction program at Erasmus MC University Medical Center. The training program consisted of 3 supervised training sessions per week lasting 60 to 90 minutes, during a 12-week period. The sessions consisted of 3 components and were preceded by a warm up of 5 minutes and completed by a 5-minute cool down. The first component was endurance training on equipment of choice at 60% of patient maximum heart rate. This was followed by 7 resistance exercises, with an initial training weight of 70% of 4 repetitions

maximum. Patients were trained with 3 sets of 15 to 20 repetitions. The training weight was adjusted when a patient was capable of executing an exercise in 3 sets with 20 repetitions. The third part consisted of core stability exercises. The first training session was supervised by 1 of 2 researchers from Erasmus MC University Medical Center (L.E.M.vdB., M.M.F.), who subsequently attended each training site every 2 weeks to monitor the proper conduct of the program.

MEASUREMENTS AND OUTCOME MEASURES

To assess the effects of the program, each patient visited the Erasmus MC University Medical Center at baseline and after 12 and 24 weeks. Fatigue, pain, and patients' functioning at the activity and participation level were assessed using questionnaires, and the ActiGraph GT3X device was used to measure the amount of physical activity.

FATIGUE

The severity of fatigue and its impact on an individual's daily functioning were assessed using the Fatigue Severity Scale (FSS). The total FSS score is the median of the 9 item scores and ranges from 1 (no signs of fatigue) to 7 (most disabling fatigue). Scores ≥4 are indicative of fatigue, and scores ≥5 are indicative of severe fatigue [11, 14]. We used the validated Dutch translation of the FSS[14].

PAIN

Two items in the questionnaire were dedicated to assessing the presence of pain/cramps (Are you suffering from pain or cramps?: yes/no) and their severity (How severe is your pain or cramp?: very mild, mild, moderate, severe, very severe).

ACTIVITY LEVEL

Functioning at the activity level was further subdivided into motor function and the amount of physical activity patients engaged in. Four tests were included. The first was the 6-minute walk test (6MWT) [15]. The second was the Quick Motor Function Test (QMFT) [16]. The third was the Rasch-built Pompe-specific Activity Scale (R-PAct) [17]. This scale covers 18 activities of daily living reported to be the most important and limiting activities for patients with Pompe disease, ranging from combing hair to running. Response options are as follows: not able; able, but with difficulties; and able without difficulties. The R-PAct score is the median item score and is translated to a scale from 0 to 100, with higher values representing better functioning[17]. Finally, all patients were fitted with an ActiGraph GT3X accelerometer to provide objective measures of the amount of physical activity they engage in. Patients were instructed to wear the ActiGraph, mounted on an elastic belt around the waist, with the unit positioned over one of the hips during waking hours. The ActiGraph monitors were set to activity counts in triaxial mode, using a 10-second epoch, which were reintegrated to 60 seconds for analyses. Nonwear time was assessed using a minimum of 60 minutes of consecutive zero counts allowing up to a 2-minute tolerance of nonzero counts. A minimum of 8h/d of wear time on at least 3 days was required to be included in analysis [18].

HEALTH STATUS

Patients' health status was assessed using the Medical Outcomes Study 36-Item Short-Form Health Survey version 2 [19]. Norm-based scores were calculated for 2 summary scores: the physical component summary (PCS) and mental component summary (MCS) scores [20]. The scores vary between 0 and 100, with higher values representing better function [21]. A score of 50 represents the general population mean, with an SD of 10.

AEROBIC FITNESS, MUSCLE STRENGTH, AND CORE STABILITY

Three types of test were done to assess functioning at the body function and structure level[9]: (1) aerobic fitness was determined by measuring the maximum oxygen uptake and maximal workload through an incremental cycling test (cyclo ergometer) to exhaustion [22]; (2) muscle strength was measured by handheld dynamometry as described previously [2]; and (3) core stability was evaluated before and after training by measuring time in balance (s) for each of the 4 core stability exercises of the training program[23, 24].

STATISTICAL ANALYSIS

Median differences in the outcomes parameters before and after the intervention were compared using the Wilcoxon signed-rank test for paired samples. For the comparison of dichotomous outcomes we used the chi-square test.

To assess the extent to which functional measures were related to the direct training goals (ie, aerobic fitness, muscle strength, core stability), we investigated the correlations between changes (before vs after training) in the outcome measures of different ICF domains with the Spearman correlation coefficient. Significance level was set at $P<.05$. Statistical analyses were performed using SPSS version 20 for Windows.

RESULTS

PATIENT CHARACTERISTICS

Twenty-three of the 25 patients enrolled in this study completed the training program. Two patients withdrew from the study because it was too time consuming for them. The median age of the participants was 46 years, and they had been treated with ERT for a median of 3 years (table 1).

Table 1 | Patient characteristics at baseline

Characteristics	**Total group (N=23)**
Gender, n male (%)	12 (52%)
Age *(yr),* median (range)	46 (20;71)
Disease duration *(yr),* median (range)	16 (6;32)
ERT duration *(yr)* median (range)	3.1 (1.3;6.5)
Training sessions (max. 36)	32 (24;36)
SF-36, PCS	40 (24-53)
SF-36, MCS	56 (25-69)

Abbreviation: SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey.

Table 2 shows the outcome measures at the body structure level as reported by van der Berg [25].

Table 2|Outcome measures at body function & structure level; reported by vd Berg [25]

	Before training	After training	p-value*
Aerobic fitness (maximum oxygen uptake; % of normative) (n=22)	69 ± 17	76 ± 18.0	<0.01
Muscle strength (HHD sum score of all muscles % of normative)	87.3 ± 7.3	88.6 ± 7.6	0.01
Core stability (average of all items ‡) (s)	15 (0.0-96.2)	29 (0.0-88.3)	<0.01
6MWT (*m*) (n=22)	492 ± 89	508 ± 97	0.01
Muscle function (total score QMFT) (n=22)	51 ± 8.1	51 ± 8.5	0.65

NOTE. Values are mean ± SD or as otherwise indicated. Abbreviations: HHD, hand held dynamometry; QMFT, quantitative motor function test, 6 MWT: six minute walk test * For the difference before and after training (paired samples t-test) ǂ Maximum oxygen uptake, 6MWT, and QMFT score were not available for 1 patient. ‡ Core stability: sum score of all items= (back bridge+ prone bridge+ left side bridge+ right side bridge)/4

EFFECTS OF 12 WEEKS OF TRAINING

Fatigue decreased from a median FSS score of 5.33 before training to 4.78 after 12 weeks of training (P=.001) (table 3). Before training, 77% of the patients were fatigued (FSS score ≥4), and 59% were severely fatigued (FSS score ≥5). After completing the training program 74% (17/23) of the patients were fatigued, and 44% (10/23) were severely fatigued.

Table 3 | Changes in Fatigue, pain, activity and participation

Outcome measure	Before training	After training	P *
Fatigue (FSS score)	5.3 (2.11;6.56)	4.8 (1.78;6.67)	0.01
Pain, number (%)	13/23 (56.5%)	5/23 (21.7%)	0.04
Motor function (R-Pact score)	70 (54;100)	70 (48;89)	0.49
Volume of physical activity (Actigraphx 10^3 in counts; n=16)	484,7 (163,4; 709,8)	418,3 (151,2; 905,3)	0.21
Qol (SF-36, PCS score)	40 (24;53)	42 (21;51)	0.86
Qol (SF-36, MCS score)	56 (25;69)	59 (34;69)	0.06

NOTE. Values are medians (ranges) or as otherwise indicated. Abbreviations: QOL, quality of Life; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey. *For the difference before and after training (χ2 test for proportions and Wilcoxon signed-rank test for continuous data).

The number of patients reporting pain also decreased after training (13/23 vs 5/23; P=.04). Before training, 7 patients reported moderate pain, and 6 reported mild pain. After training, 5 patients reported mild pain, and none reported moderate pain.

No significant differences were observed in self-reported motor function, as measured by the R-PAct. The amount of physical activity, measured as the mean number of counts per day using the ActiGraph device, did not change at the group level (table 3); 9 patients showed a decrease, and the remaining 7 patients showed an increase.

Median scores and ranges for the PCS and MCS scores are also shown in table 3. The MCS showed a borderline significant change from 56.1 to 59.1 (P=.06).

CORRELATIONS BETWEEN OUTCOME MEASURES

Table 4 displays the correlations between changes in the trained parameters (aerobic fitness, muscle strength, core stability) at the body structure level and the parameters at the remaining levels of the ICF model. Improvements in pain and fatigue were not correlated to changes in any of the trained outcome measures.

The improved distance walked on the 6MWT significantly correlated with improvements in both aerobic fitness (r=.495; P=.02) and muscle strength (r=.448; P=.04); the QMFT showed a borderline significant correlation with aerobic fitness (r=.414; P=.06).

At participation level, changes in the MCS were correlated with improvements of aerobic fitness (r=.657; P<.001) and muscle strength (r=.517; P=.01). No other significant correlations were found. Improvements in core stability were not associated with any of the outcomes.

Table 4 | Correlations between changes in different outcome measures

Body level (van den Berg[25])	**Fatigue**	**Pain**	**Activity level**				**Participation level**	
	FSS	**Yes/ No**	**Motor Function**			**Amount of Physical Activity**	**QoL (SF-36)**	
			6MWT	**QMFT**	**R-Pact**	**AG**	**PCS**	**MCS**
Aerobic fitness (VO2max)	-.149	.325	.495*	.414	-.120	-.120	-.173	.657ŧ
Muscle strength (HHD)	-.021	.286	.448*	.310	.005	.005	-.282	.517*
Core stability	.060	-.161	.245	-.072	.209	.271	-.042	.31

Abbreviations: 6 MWT, 6 minute walk test; AG, Actigraph; FSS, fatigue severity score; HHD, hand-held dynamometry; MCS, mental component summary; PCS, physical component summary; QMFT, quick motor function test; QoL, Quality of Life; R-Pact, Rasch-built Pompe-specific Activity scale; VO2max, Maximum oxygen uptake

*P<0.05, ŧP<0.01

DISCUSSION

We previously showed our combined training program to improve aerobic fitness, muscle strength, core stability, and distance walked in a group of mildly affected adults with Pompe disease[25]. This study adds that such a comprehensive exercise intervention program also has a positive effect on fatigue and pain scores and may improve mental health. Our training program did not affect the quality of motor function or the amount of physical activity. To gain insight into the extent to which functional measures were related to the direct training goals, we also studied the correlations between the different domains of the ICF model. Changes in fatigue and pain were not associated with improvements in aerobic fitness and muscle strength.

Fatigue is an important feature of late-onset Pompe disease and has been reported as one of the disease's most disabling symptoms [11]. Our training program significantly decreased the level of fatigue by 0.5 points (FSS score, 5.33 to 4.78; P=.001). Although the clinical relevance of this change can be discussed, we feel that this change of almost 10% is clinically important. It has to be realized that this is the average change and that the proportion of severely fatigued patients dropped by 15 percentage points. Similar to the study of Gungor et al. [12] we found no correlations between reductions in fatigue and improvements in muscle strength or in the other trained parameters. Therefore, this finding does not support our assumed chain of subsequent effects, with exercise leading to improved exercise capacity, which in turn lowers physical load in daily life, resulting in less fatigue. Training may therefore affect fatigue through another route. For example, it has been suggested that exercise positively influences the neuroendocrine system and levels of neurotransmitters,[26] which may influence both peripheral and central fatigue.

Pain is another complaint frequently reported by patients with Pompe disease and impacts on their well-being and quality of life[13, 27, 28]. Our training program positively affected pain, reducing the proportion of patients experiencing pain from 57% at baseline to 22% after training. Pain in Pompe disease may have various causes, including short-term peak loading of weakened or atrophied muscles and more long-term mechanical stress. Irrespective of the explanation, the pain reduction itself is important for patients with Pompe disease.

Although the distance walked improved after training, the program did not improve the other motor function parameters, either self-reported (R-PAct and PCS) or clinically observed (QMFT) [25]. Training thus seems to have a positive effect on the speed of movement, but not on the quality of motor function (ie, how these activities are performed). It is unlikely that an improvement in speed without improvement in how these movements are executed is clinically useful for patients. It is nevertheless also possible that the period of 12 weeks is too short to achieve changes in the quality of motor function. Finally, task-specific training complementary to exercise therapy, shown to have added value in post stroke patients [29, 30] may help to improve this.

The observed correlation between the improved walking distance on the 6MWT with both endurance and muscle strength can be explained by the 6MWT being a combined assessment of cardiac, respiratory, circulatory, and muscular capacity [31].

Little information is available about the amount of physical activity of patients with Pompe disease (ie, how active these patients are in daily life). Prior to training, we found that the level of physical activity, expressed in mean number of counts per day, was considerably lower (203.4 × 102) than in healthy controls (269.7 × 102) and comparable with the level observed in mildly affected patients

with multiple sclerosis (204.7 × 102) [32].This outcome did not improve with training. In addition to the reasons previously mentioned, it reflects habitual behaviour that may be difficult to change. On the other hand, the improvement observed in a subset of patients (all scoring is better on the outcome measures compared with the other patients at baseline) may suggest that a relatively high level of functioning is required to achieve an effect on this outcome measure.

STUDY LIMITATIONS

Our study is the first to focus on the effects of training in patients with Pompe disease on a wider range of parameters, including activity and participation. The observed changes were relatively small in our study. This might be the result of the short training period or the training having a limited effect only. At what point a difference becomes clinically meaningful (minimal clinically meaningful difference) has not been determined for the measures we used in this study, except for the Medical Outcomes Study 36-Item Short-Form Health Survey, and the observed effects should be interpreted with caution.

Our study design does not allow us to exclude the possibility that other factors may have played a role in the observed effect. Originally, the study was set up as a crossover trial, but all of the patients who started training at the beginning of the study continued to do so after the crossover point, and it was decided to analyse this as a pre-post study [25]. The original design did allow us to exclude that the improvements in strength and endurance were the result of ERT[25].

Because of the small sample size and explorative character of the study, we did not adjust for multiple comparisons (for testing a number of outcome measures). Results are therefore indicative rather than hard conclusions.

Other points of concern are the relatively short duration of the study and the small number of patients. Longer training and follow-up is needed to confirm if continued exercise is required to maintain the effects of training and to see if patients can continue training independently outside of the program.

CONCLUSIONS

This study suggests that our combined training program, which aimed to increase aerobic fitness, muscle strength, and core stability also leads to improvements in fatigue and pain and may improve mental health in patients mildly affected with Pompe disease. The observed improvements in pain and fatigue were not determined by aerobic fitness, muscle strength, or core stability. Further research is needed to understand the functional consequences of Pompe disease and the underlying mechanisms of exercise.

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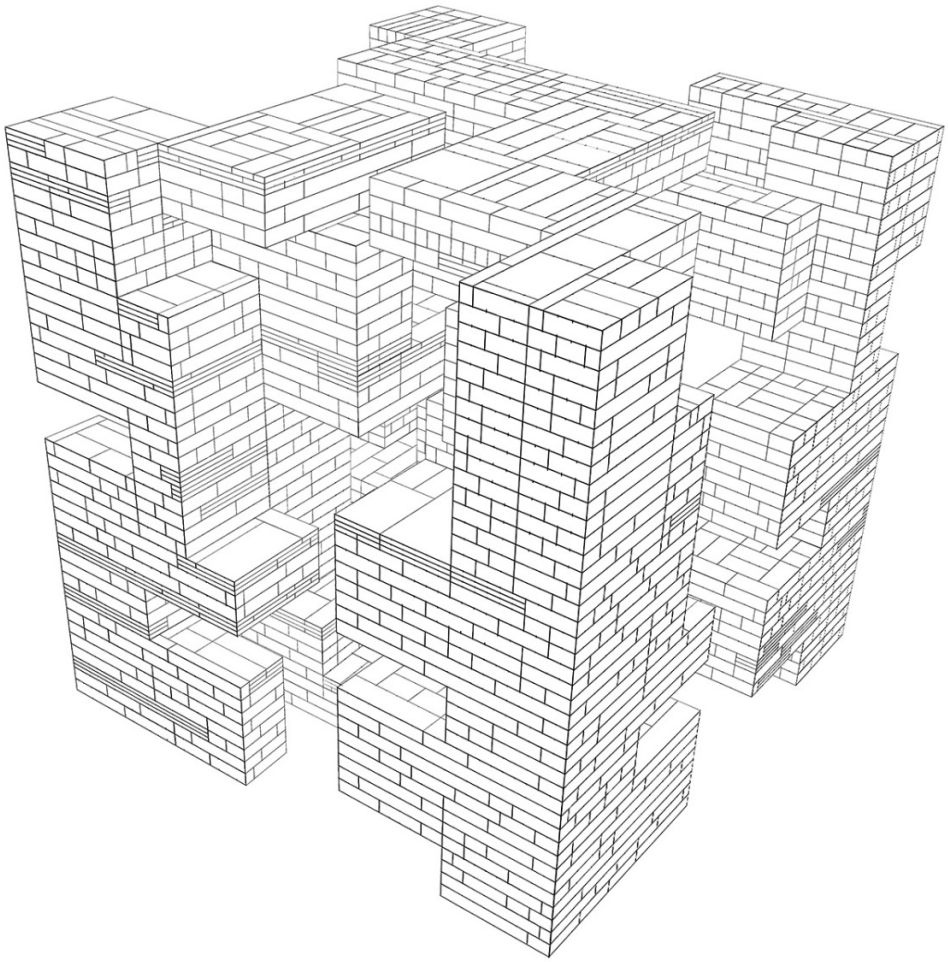

CHAPTER 05

ASSOCIATION OF MUSCLE STRENGTH AND WALKING PERFORMANCE IN ADULT PATIENTS WITH POMPE DISEASE

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ABSTRACT

BACKGROUND

The loss of the ability to walk is among the most prominent signs of Pompe disease. The associations with muscle strength have not been described.

OBJECTIVE

The objective of this study was to estimate the associations of walking performance with muscle strength in four specific lower extremity muscle groups along with other factors in adult patients with Pompe disease.

DESIGN

This was a single-center cross-sectional study.

METHODS

Muscle strength (hand-held dynamometry of hip flexion and abduction and knee extension– and flexion) and walking performance (unable, able with aids, waddling gait, normal gait) were assessed in 107 patients at their first visit. Relationships between walking performance and muscle strength were studied by multivariate analyses and regression modelling. Age, gender, body mass index (BMI), disease duration, and use of ventilator support were taken into account as potential confounders. We transformed the results into a nomogram to allow the probability of a patient having a certain level of walking performance to be calculated based on the values of the independent variables.

RESULTS

Walking performance declined significantly with decreasing muscle strength of hip flexion and abduction and knee extension– and flexion. The final selected model, including strength of the hip abductor and knee extensor, BMI, age, gender, and use of ventilation, predicted 66% of the cases accurately.

LIMITATIONS

These results are based on cross-sectional data and do not predict future changes.

CONCLUSIONS

In adult patients with Pompe disease, walking performance can be explained by muscle strength, BMI, age, gender, and ventilation use. Our model gives insight into how a patient is expected to walk based on his or her risk factors and serves as a starting point to unravelling factors associated with walking performance, and ultimately to developing a prognostic model.

INTRODUCTION

Pompe disease is a rare inheritable metabolic myopathy. It is caused by deficiency of the lysosomal enzyme acid α-glucosidase which is needed to breakdown glycogen in the lysosomes. As a result, glycogen accumulates in several tissues, especially muscle cells. The disease presents as a broad clinical spectrum, with variable organ involvement, age of onset and severity. The most severe form, seen in infants, results in death within the first year of life, while the disease progresses more slowly in children and adults [1].

In adults, Pompe disease is characterized by limb-girdle weakness and weakness of respiratory muscles (including the diaphragm). Patients develop Duchenne or Trendelenburg signs or a swayback posture. Eventually patients lose the ability to walk and become wheelchair and/or respirator dependent.

The loss of the ability to walk is one of the most prominent signs and debilitating effects of Pompe disease and has been shown to be an important factor in determining patients' quality of life [2]. In general, retaining the ability to walk is important to maintain independent from caregivers [3, 4].

Reduced walking performance has shown to be related to decreased skeletal muscle strength in several populations, including patients with related neuromuscular diseases and elderly [5-9]. However, the associations between walking performance and muscle strength have not been described for patients with Pompe disease. Results from studies in other neuromuscular diseases cannot automatically be generalized to these patients as the distribution of muscle weakness, and thus its effects on walking performance, differs [9]. Also other risk factors, such as age, BMI and respiratory status that might contribute to a

reduced walking performance are not well understood in patients with Pompe disease.

By modeling the relationship between walking performance on the one hand, and muscle strength and associated risk factors on the other, it will be possible to determine a patient's expected position in the spectrum of walking performance. This can give the clinician a better feel for where the patient is in the disease process. Importantly, the model can serve as a starting point to further our understanding of the factors that determine walking performance in Pompe disease, and ultimately to develop a prognostic model for larger patient care planning efforts among the integrated rehabilitation team.

The aim of our study was to estimate the associations of walking performance with muscle strength of specific lower extremity muscle groups and with other factors in adult patients with Pompe disease.

METHODS

PARTICIPANTS

Adult patients with a confirmed diagnosis of Pompe disease were included in this study. All patients were first seen between December 2003 and August 2012 at the Center for Lysosomal and Metabolic Diseases of the Erasmus MC University Medical Center, Rotterdam, the national referral center for patients with Pompe disease in the Netherlands. Patients were excluded if they had co-morbidities that affected their walking performance.

On visiting the center, patients were subjected to a standardized set of outcome tests, including assessment of muscle strength and motor function tests

encompassing the ability to walk. Data from the patients' first visit to the center was analyzed retrospectively. We also recorded age, gender, height, weight, and disease duration (time since diagnosis) for each patient. All patients signed informed consent.

Outcome Measures

Walking performance was classified in four categories (unable to walk, walking with aids, walking without aids but with a waddling gait, or walking without aids and with a normal gait) according to the item "walking 10 meters" of the Quick Motor Function Test (QMFT) [10]. This item was assessed by asking patients to walk a 10-m course at their usual pace. Use of aids (canes or walkers) was allowed for this test, but patients were challenged to achieve the maximum performance, i.e., those who used a wheelchair but could still walk 10 meters were asked to do so. Patients were classified as unable to walk when they were fully dependent on a wheelchair (i.e. they could not walk more than a few steps without a walking aid)). Patients who used a wheelchair but were capable of walking 10 meters were scored as "able to walk with aids". Normal gait was considered as a gait pattern without a Trendelenburg or Duchenne sign or swayback.

Skeletal muscle strength exerted during maximal voluntary eccentric contractions was measured by hand-held-dynamometry (HHD) (Cytec dynamometer, Groningen, the Netherlands [a]). The following lower proximal muscle groups were tested using the break test technique: [11, 12] hip flexors, hip abductors, knee flexors and knee extensors. Specifics of the test positions, stabilization and dynamometer placement have been described elsewhere [13]. Muscles were tested separately for each leg and values were averaged for the two legs. The absolute HHD values were used and expressed in Newtons. All measurements

were carried out by three physicians specially trained to perform HHD and connected to our center.

DATA ANALYSIS

Median muscle strength values were plotted against the four levels of walking performance using box plots. Differences in muscle strength were assessed using the Kruskal-Wallis test. When this was significant, the Mann Whitney test was used to identify which of the groups differed. Ordered logistic regression was used to build a model describing the independent variable walking performance, based on the dependent variables: muscle strength of the four lower extremity muscle groups, age, gender, body mass index (BMI), disease duration and use of ventilator support [3, 14, 15]. A step backward method was used, starting with a full model containing all possible independent variables. Variables that did not contribute to the model were excluded at a cut-off significance level of 0.20.

Internal validation of the (full and subsequent) models was assessed using the Bootstrap technique with 1000 samples. As measures of predictive ability we use the area under the receiver operating characteristic curve (AUC, discriminative ability), Nagelkerke's R^2 (goodness of fit), the calibration slope, and the Brier Score (predictive accuracy). The most parsimonious model that performed satisfactorily in the validation step was reported here.

Next, based on this model, a nomogram was constructed which allows the chance of being in one of the four levels of walking performance to be calculated directly from given specific values of the independent variables.

Differences in patient characteristics and muscle strength were tested using SPSS for Windows (release 21.0; SPSS, Inc., Chicago, IL). All other statistical analyses were performed in R: A Language and Environment for Statistical Computing,

version 3.2.2 using the rms package (rms: Regression Modelling Strategies, Frank E Harrell Jr, R package version 4.4-1, 2015). Visualization was performed using GraphPad Prism (version 5) and the rms package.

RESULTS

PARTICIPANTS

During the study period 108 adult patients with Pompe disease were first seen at the national referral center and examined. One patient was excluded from the analyses because this patient had Pompe disease in combination with spina bifida, both interfering with muscle strength.

Table 1 presents the characteristics of the 107 included patients at their first visit to the center. Patients had a median age of 50 years (minimum 25; maximum 76) and had experienced symptoms for a median of 15 years. 28% were ventilator dependent. In terms of walking performance, 11% were fully dependent on a wheelchair, 28% used walking aids, and 43% walked with an abnormal gait without aids and the remainder (18%) had a normal walking pattern. None had started treatment with ERT at time of examination for this study.

Table 1| Characteristics of 107 Adult patients with Pompe Disease (First Visit to Referral Center)

Patient Characteristics at First Visit	dy Population (n = 107)
Gender (male), no (%)	55 (51.4%)
Age (years), median (minimum-maximum)	50 (25-76)
BMI (kg/m^2), median (minimum-maximum)	24.1 (15-48)
Disease duration (years), median (minimum-maximum)	15 (2-48)
Walking performance, no (%)	
- Unable to walk	12 (11.2%)
- Walking aids	30 (28%)
- Walking without aids with waddling gait	46 (43%)
- Normal gait	19 (17.8%)
Respiratory support at first visit, no (%)	
- No ventilator use	77 (72%)
- Ventilator dependent	30 (28%)

ASSOCIATION BETWEEN WALKING PERFORMANCE AND LOWER PROXIMAL MUSCLE STRENGTH

Figure 1 shows the differences between each of the consecutive walking categories in strength of the hip flexors, hip abductors, knee extensors and knee flexors. Walking performance declined with decreasing muscle strength. This was most obvious for the hip flexors and hip abductors, where muscle strength differed significantly between each consecutive level of walking performance ($p <$ 0.01). For knee extension, no significant difference in strength of the knee extensors was found between patients with a waddling gait and those walking normally. For strength of knee flexors there were no differences between any of the consecutive walking categories.

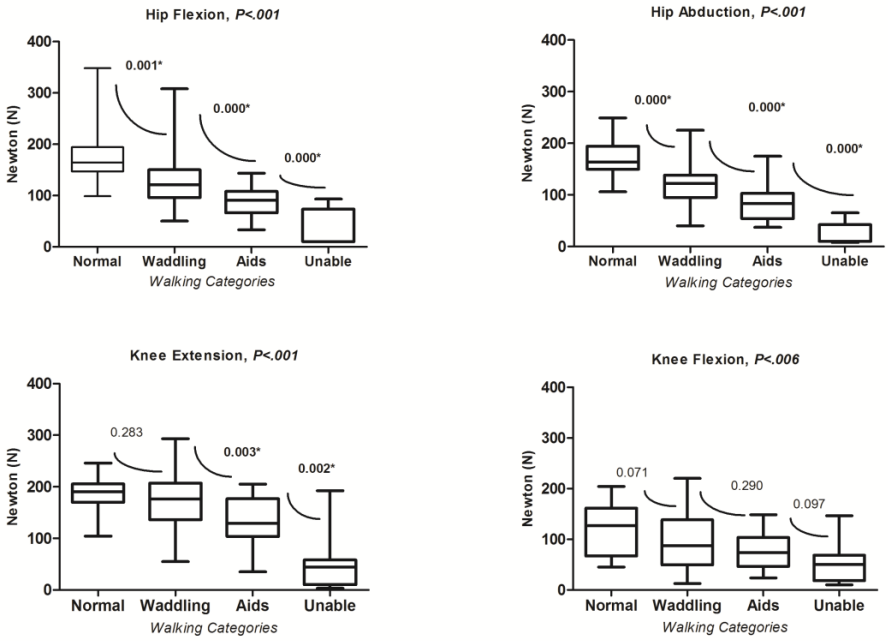

Figure 1 |Relationship between lower extremity muscle strength (expressed in Newtons) and walking performance. Unable = fully dependent on a wheelchair; aids = walking with walking aids; waddling = waddling gait; normal = normal gait pattern. The *P*-value for differences between any of the groups (Kruskal-Wallis test) is shown at the top of each graph, while differences between adjacent groups (Mann-Whitney test) are indicated by the bridging lines (* = significant differences between adjacent groups).

Table 2 displays the patients' muscle strength values and other risk factors across the four walking categories. Besides reduced muscle strength, patients with more impaired walking performance were older, had been symptomatic for longer and were more often ventilated compared to those

Table 2 | Characteristics and Muscle Strength Across the Four Walking Categories [a]

	Normal (n = 19)	Waddling (n = 46)	Aids (n = 30)	Unable (n = 12)	P value
Muscle strength (N)					
- Hip flexion	164.5 (99-348)	121.1 (50-308)	91.0 (33-144)	10 (10-93)	**<.001** [b]
- Hip abduction	163.5 (106-249)	121.8 (40-225)	83.5 (37-175)	10 (7-65)	**<.001** [b]
- Knee extension	190.5 (105-246)	176.5 (55-293)	129.1 (35-205)	49.0 (3-193)	**<.001** [b]
- Knee flexion	126.8 (45-204)	87.3 (13-220)	73.4 (24-149)	52.2 (10-147)	.006 [b]
Characteristics					
- Age (yrs)	45.0 (25-72)	46.5 (25-68)	54.0 (26-71)	59.0 (33-76)	**<.001** [b]
- BMI	23.1 (19-29)	24.2 (17-48)	25.2 (20-38)	23.2 (15-28)	.074
- Disease duration (yrs)	1.0 (0-27)	1.5 (0-19)	13.0 (0-30)	22.0 (0-32)	**<.001** [b]
- Ventilation *(*% yes)	5.3	15.2	60.0	83.3	**<.001** [b]
Gender (% male)	36.8	54.3	43.3	83.3	.059

[a] Continuous variables are shown as median and ranges (minimum-maximum) and compared with the Kruskal-Wallis test. Categorical values are expressed as percentages and p-values calculated with Chi square analysis.
[b] significant differences between one or more of the walking categories

with normal / less impaired walking performance. Also higher BMI and male gender seemed to be more frequent in the more impaired patients.

Stepwise backward elimination of the variables in Table 2 ($P < 0.20$) resulted in an ordered logistic regression model containing the variables strength of the hip abductors and knee extensors, gender, age, ventilation use and BMI. This was the most parsimonious model and also performed well on internal validation (AUC for discriminative ability: 0.76; Nagelkerke's R2 for goodness of fit: 0.66; calibration slope: 0.86; Brier score for predictive accuracy (lower is better): 0.14). Higher strength of the hip abductors (OR:1.042; CI [1.026-1.057]) and knee extensors (OR:1.011; CI [1.001-1.022]), lower age (OR:0.968; CI [0.931-1.005]), lower BMI (OR:0.837; CI [0.753-0.930]), female gender (OR:0.365; CI [0.137-0.972]) and not using ventilator assistance (OR:4.540 CI [1.379-14.950]) are associated with the probability of being in a better walking category. The eAppendix provides the regression and validation results for the different models that were generated, as well as further information on the interpretation of the validation coefficients.

Figure 2A shows the results of this model transformed into a nomogram. This visualization of the model allows the probability of being in one of the four categories of walking performance to be calculated directly based on given values of the independent variables. The range of each independent variable is related to a corresponding number of points on a linear scale. The sum of the corresponding points for each variable (total points) corresponds with the probability for being in each of the four walking categories. Two example calculations, based on two of our patients, both with an observed waddling gait, are shown in Figure 2B.

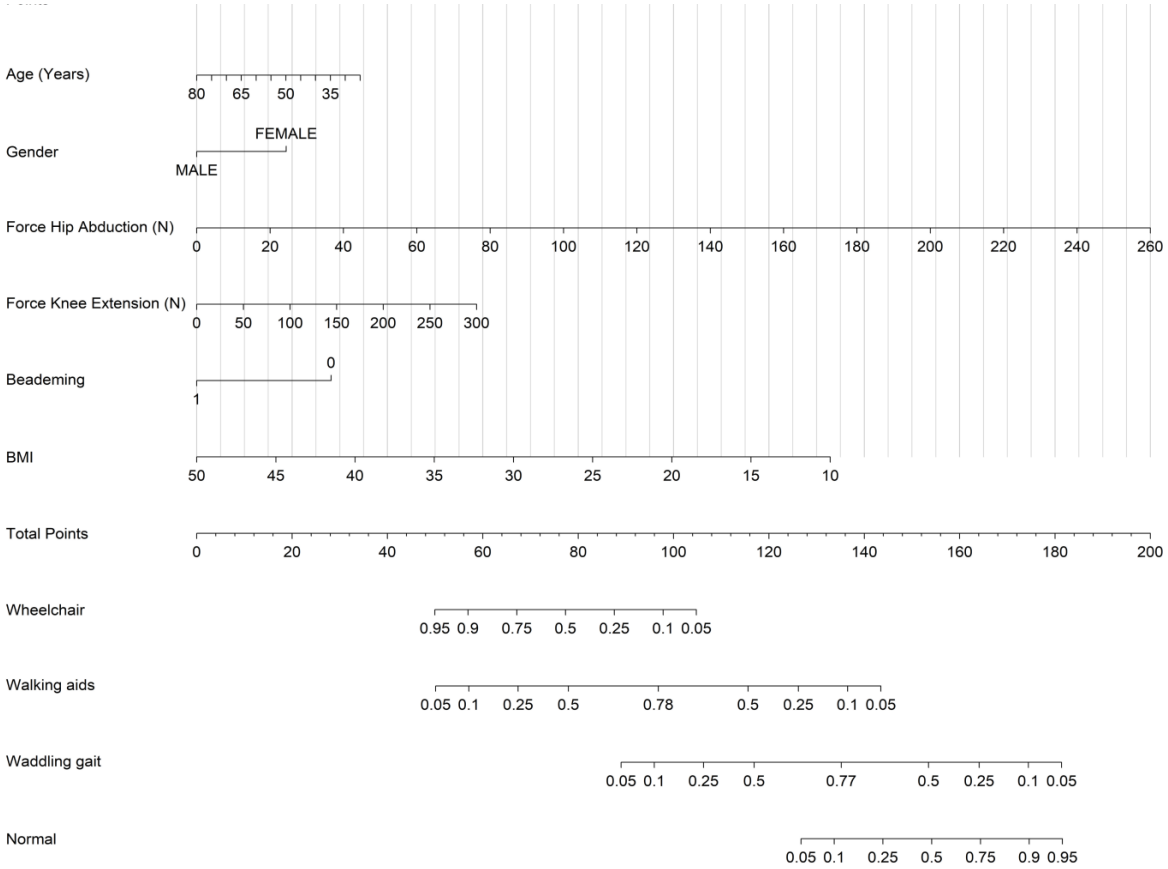

Figure 2A | nomogram for predicting the change of being at one of the four categories of walking performance in patients with Pompe disease

Case report patient I			Case report patient II		
Variables	Walking category	chances	Variables	Walking category	chances
• 42 yr • female • HA strength 128 N • KE strength 147N • No ventilation use • BMI 22 kg/m^2		25%	• 50 yr • male • HA strength 95N • KE strength 175N • No ventilation use • BMI 24 kg/m^2		<5%
		70%			55%
		<5%			40%
		<5%			<5%

Figure 2B |The probability of being in one of the four categories of walking performance can be calculated from the nomogram as follows. First, for each independent variable, the value is projected upwards onto the 'Points' scale to give the corresponding points. Next, these points are added and the total points are projected downwards from the 'Total points' scale to the scales giving the corresponding probabilities for being in one of the four walking categories.
For example, case report I is a 42-year-old woman with a hip abduction (HA) strength of 128 Newtons and knee extension (KE) of 147 Newtons who does not use a ventilator and has a BMI of 22 kg/m2. In the first step, we project these values onto the top 'Points' scale, counting 12 points for age, 9 for being female, 49 for HA strength, 14 for KE strength, 14 for being ventilator independent, and 45 for BMI. The total points value is 143. When drawing a vertical line downward, this gives a 70% chance of walking with a waddling gait, 25% chance of a normal gait, and <5% chance of other options.

DISCUSSION

In adult patients with Pompe disease walking performance declines with decreasing strength of the lower extremities. This study shows that a patient's probability to have a certain level of walking performance can be calculated based on muscle strength and a number of other risk factors. The model we describe here enables clinicians to compare a patient's actual walking performance to that expected based on his risk factors, and thereby counsel patients on their current disease status and possible supportive measures. It should be further expanded to encompass other factors and ultimately develop a prognostic model.

Walking performance declined most obviously with decreasing strength of the hip flexion and abduction. The strength of knee extension varied significantly between three of the four walking categories only, while knee flexion didn't distinguish between any of the four consecutive categories. This is consistent with findings based on muscle-driven simulation which showed that gait was most affected by weakness of hip abductors and hip flexors, as well as plantar flexors which are not usually affected in adult patients with Pompe disease [16]. Observed muscle strength values overlapped considerably between the consecutive walking categories, indicating that other patient characteristics, e.g. gender and BMI, may affect walking performance also [14, 15, 17]. Concerted contraction of muscle groups as a compensation for weakness may play a role as well [16]. To compensate for weak quadriceps muscles a hip extensor might be included for knee extensor strategy, i.e. using the two joint characteristics of the hamstring muscle to move the knee towards extension [18]. Therefore, we developed a multivariate regression model to describe walking performance.

The probability of being in one of the walking categories can be calculated best based on strength of the hip abduction and knee extension, age, gender, BMI and respiratory support. From the four lower extremity muscle strength groups, only hip abduction and knee extension contributed to the final model because of the interdependence between the four groups. Despite disease duration being associated with disease severity [19], this variable didn't contribute to the model after correcting for age. In our model women had a higher chance of being in a better walking category. These gender differences were also found by De Vries et al. [20].

One of the perspectives of creating a multi-variate model is the application in clinical practice, and therefore the model was transformed into a nomogram. By doing this, a patient's chance to have a certain level of walking performance can be calculated based on his risk factors. While a patient's actual walking performance can be observed, the nomogram allows a clinician to compare this to the probability of being in the four walking performance categories based on the patient's muscle strength and risk factors. This comparison has several potential clinical benefits. For example, in case that the expected (i.e. the walking category with the highest probability) and observed walking performance are the same, there are two options: 1) the probability of the expected walking category might be the clearly highest, or 2) the probability of the expected walking category is quite close to the probability of an adjacent walking category. In the first condition, a patient can be reassured and has not to be prepared on a change to another walking category. In the second condition, a patient can be advised to do strength training and/ or lose weight in order to prolong this particular ambulant status. In case of a discrepancy between observed and expected walking performance, this might draw the attention to the issues of overload (when the

observed walking category is “higher” than the expected one) or underload (in case of a “lower” walking category than calculated).

In the current sample, our model predicted walking performance accurately in 66% of the cases. Hence, in around 34% of the cases the observed walking performance deviated from the model results. Other explanatory factors may play a role as well. For example, one of our patients had a high chance of walking with aids (70% chance), but was observed to walk with a waddling gait (i.e. overloading). Further inspection showed us that this patient had a substantial scapula alata preventing the use of a walking stick. This comes at the price of a high fall risk and alternative solutions to walking aids need to be searched for or a wheelchair recommended. This example illustrates that further factors may need to be incorporated to accurately predict walking performance in a prognostic model. In future research, it will be important to include instrumented gait analysis in order to identify compensatory movements for core and/ or lower extremity muscle weakness.

Our analyses are based on a cohort of more than 100 adult Pompe patients, which is very large given the rarity of the disease. However, to develop an accurate model patient numbers are relatively small. Nevertheless, internal validation of the model yielded a reasonable concordance between actual and estimated walking performance, and our model predicted walking performance accurately in 66% of the cases. A lack of external validation can be regarded as a limitation of our study. The model’s validity in other cohorts of Pompe patients remains to be studied. Furthermore, the nomogram was based on cross-sectional data rather than longitudinal data, and as a consequence it does not provide information on a patient’s prognosis or future walking performance. Another limitation is related to the measurement of muscle strength. HHD values were obtained using standard testing as described and widely used [13]. Three testers (male and female) were

involved in this study, where one performed the majority of the strength tests. The inter-rater reliability was not assessed, and whether this impacts the clinically utility of the nomogram remains to be determined. Finally, in Pompe disease trunk muscles are frequently involved [15] which affect strength and performance of the lower extremities [21]. Due to the lack of objective measurements of the core strength [21] this could not be included in our model. Although plantar flexors are known to be important for gait performance we did not included these in our model. This was because they are known not to be severely affected in Pompe disease, which was supported by the data of our population, with all patients having values close to those seen in healthy people[13], which means that this would not add to the model**.**

This study shows that reduced walking performance in adult patients with Pompe disease is associated with reduced muscle strength of the lower extremities, as well as with higher age, higher BMI, being male and using a ventilator. We developed a model describing the chance to be in one of four walking categories. This model can support a clinician's subjective judgement on whether a patient - based on his risk factors- is capable of more or less than what a patient shows in terms of walking performance. Moreover, it might serve as a first step towards developing a prognostic model.

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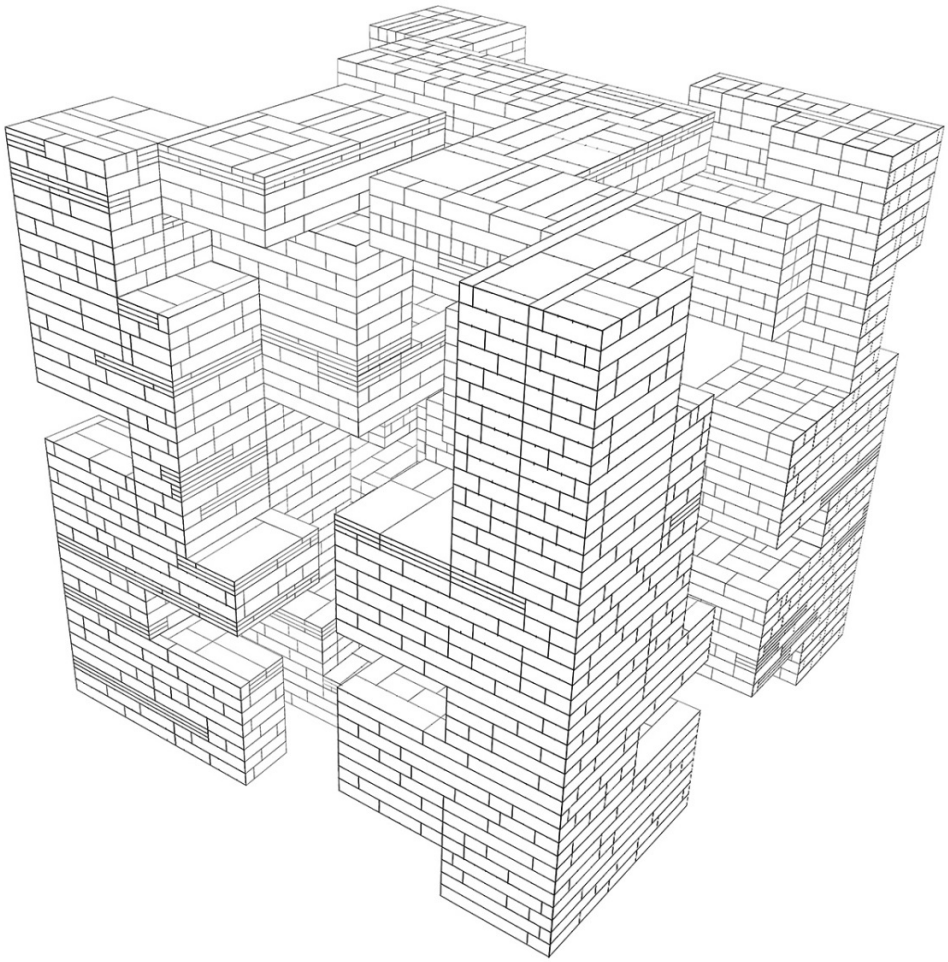

CHAPTER 06

INCONTINENCE IN POMPE DISEASE:

PREVALENCE AND REFERRAL TO PELVIC FLOOR PHYSIOTHERAPY

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ABSTRACT

Incontinence has been reported as a problem in Pompe disease. Due to its disabling symptoms treatment options should be explored. As pelvic floor muscles are also involved in this disease, pelvic floor physiotherapy (PFPT) might be beneficial. Here we assessed the prevalence of incontinence in Dutch adult patients and PFPT experiences.

In 2015/6 we asked all adults with Pompe disease in the Netherlands about urine, fecal and double incontinence and referred them, when needed, to PFPT. Patient-files from physiotherapists and retrospective patient interviews were used.

Of 121 patients, 31 reported urinary, 11 fecal and 17 double incontinence. These patients were more severely affected and had a longer disease duration than those not reporting incontinence (p=0.01-0.04). 77% of the patients reporting urinary incontinence were female; 73% reporting fecal incontinence were male. 47% of the patients were treated with PFPT. Education (100%) and pelvic floor exercises (94%) were the interventions most applied. 18/20 patients who were interviewed reported benefit from PFPT.

In conclusion, 49% of patients with Pompe disease suffer from incontinence. Interventions and assessments of PFPT vary widely. Beneficial effects were reported by 75% of the patients. Incontinence and its treatment should receive more attention in adults with Pompe disease.

INTRODUCTION

Pompe disease, or glycogen storage disorder type II, is an inheritable disorder predominantly affecting the muscles. It is caused by a deficiency of the enzyme acid alpha-glucosidase, which leads to lysosomal accumulation of glycogen. The disease presents as a clinical spectrum affecting children and adults. In adult patients, the pattern of muscle weakness typically fits a pattern of limb-girdle myopathy, with the core, hip muscles and respiratory muscles being the most severely affected [1-4]. Progression of the disease eventually leads to wheelchair and ventilator dependency. Enzyme replacement therapy (ERT), with recombinant human acid alpha-glucosidase, available since 2006, has been shown to improve or stabilize patients' skeletal muscle strength, respiratory function, walking distance and survival, but residual muscle weakness remains present [5, 6].

Pelvic floor muscles (PFM) form the caudal boundary of the limb-girdle region. So far, the involvement the PFM and the accompanying consequences have remained underexposed in Pompe disease [7]. One of the major functions of PFM is providing conscious control over the bladder and bowel; dysfunction can consequently lead to incontinence. A few studies previously reported on incontinence in adult patients with Pompe disease [8-11]. These studies pointed in particular to smooth muscle involvement of the bladder and gastrointestinal tract as the potential cause of incontinence [8, 9, 11-14]. Pathophysiologic hypotheses for incontinence in other myopathies, such as myotonic dystrophy, include striated pelvic floor muscle involvement as an important factor [15, 16]. Two MRI studies in adults with Pompe disease show that striated muscles of the pelvic floor are quite severely damaged [17, 18].

While two studies suggest that gastrointestinal symptoms, including incontinence, respond well to ERT [9, 10], our experience is that incontinence is still reported by patients who are treated with ERT [8]. In the general population, it is common practice to refer individuals who suffer from incontinence to pelvic floor physiotherapy (PFPT) [19-21], which has been demonstrated to be effective in the treatment of urinary and fecal incontinence in both men and women [22, 23]. PFPT involves, amongst others, exercises to encourage relaxation and strengthening of the pelvic floor muscles. Therefore, and seen the disabling impact on patients' daily activities and quality of life [8, 24], making it worthwhile exploring PFPT as a treatment option for incontinence in patients with Pompe disease. This has not been studied so far.

Here, we aim to describe the problem of incontinence by reporting the prevalence and characteristics of incontinence in of adult patients with Pompe disease in the Netherlands. In addition, we describe the referral to PFPT in terms of, interventions used, outcomes assessed before and after treatment. We also report how therapists and patients perceived the effects of treatment.

METHODS

PARTICIPANTS AND PROCEDURES

At the Center for Lysosomal and Metabolic Diseases of Erasmus MC University Medical Center, Rotterdam, the endorsed center of expertise for Pompe disease in the Netherlands, all Dutch patients with Pompe disease are seen on regular basis. Patients are subjected to a set of standardized tests [3, 6]. Between April 2015 and May 2016 all patients were asked about urine and fecal incontinence symptoms by a physiotherapist (MF, RvdS). Urine incontinence (UI) was defined as recurring involuntary loss of urine; fecal incontinence (FI) as recurring involuntary leakage of liquid or solid stool; double incontinence (DI) was registered when both UI and FI were reported. Patients were asked whether he/she had suffered from each type of incontinence in the past 3-6 months. We omitted reports of non-recurring loss of feces that coincided with an infection. Additionally women were asked about their maternity status. Main causes of incontinence, such as central nervous system diseases and maternity status, were asked by detailed anamnesis in each patient and their medical records were reviewed for gynecologic and urologic history. Since 2015, patients reporting any type of incontinence are offered a referral to PFPT.

All patients provided informed consent for this study as part of two larger studies [3, 6] on monitoring the disease progression and effects of ERT.

MEASUREMENTS AND OUTCOME MEASURES

Muscle strength was measured by manual muscle testing using the Medical Research Council (MRC) grading scale [25] (range 0-5; all patients were examined by one physician, EK). Specifics of the tested muscles have been described elsewhere [3]. Pulmonary function (Forced Vital Capacity (FVC) was measured in sitting and supine position. Results were expressed as a percentage of predicted normal values [26]. The postural drop is the relative difference between FVC in sitting and supine position, which is an indicator of diaphragm weakness when larger than 25% [27].Participation in daily life was measured using the Rotterdam handicap Scale (RHS), with a score range from 9 (worst) to 36 (best) [28, 29].

REFERRAL TO PFPT

We offered referral to pelvic floor physiotherapy PFPT to all patients with incontinence. Between April 2017 and May 2018 we asked the physiotherapists to provide the files of the referred patients. We assessed this information regarding intervention(s) used, the assessments done before and after treatment (physical examination of pelvic floor muscle tone and/ or incontinence questionnaires), and outcomes thereof. In addition, we also contacted the patients by telephone to ask whether they were satisfied with PFPT on a numeric rating scale (0: unsatisfied - 10: very satisfied) and perceived an improvement in their incontinence symptoms on a 5-point Likert scale (0: free of symptoms; 1: slight decrease of symptoms; 2: no change in symptoms; 3: slight increase of symptoms; 4: incontinence worsened).

ANALYSIS

We calculated the prevalence of urinary and faecal incontinence in our cohort. Characteristics of patients with and without incontinence were compared using Pearson Chi-2 test for categorical and Mann Whitney for continuous data. The Pearson Chi-2 test and Kruskal-Wallis were used for comparing the three incontinence groups (UI, FI and DI).

Descriptive statistics were performed with SPSS 24.0 for Windows software (SPSS, Inc., Chicago IL).

RESULTS

PATIENT CHARACTERISTICS AND PREVALENCE OF INCONTINENCE

A total of 121 patients visited our clinic between April 2015 and May 2016 and were asked about incontinence symptoms. Patients had a median age of 54 years (range 20-83); 45% was male (Table 1). Forty two patients were wheelchair bound and forty were ventilator dependent; twenty seven patients were both ventilator and wheelchair dependent. Of the 121 patients, 98 were treated with ERT (20 mg/kg, biweekly), with a median treatment duration of almost 8,5 years (103 months, range 3-204).

In total 59 patients (49%) reported incontinence: 31 (52%) had urinary incontinence, 11 (19%) had fecal incontinence while 17 (29%) were incontinent for both (double incontinence). When stratifying for sex, we found that the overall prevalence of urine incontinence was 32% in males vs. 46% in women,

Table 1 | Clinical and demographic characteristics of 121 Dutch adult Pompe patients reporting incontinence symptoms versus those not reporting incontinence; and by type of incontinence symptoms.

		Incontinence problems yes/no Number (%) or median [range]			Type of incontinence problem Number (%) or median [range]			
	All 121 patients	No 62 patients (51%)	Yes 59 patients (49%)	p-value	UI 31 patients prevalence (52%)	FI 11 patients prevalence (19%)	DI 17 patients prevalence (29%)	p-value #
Patient characteristics:								
Gender				0.63				0.04 *
- Male	54 (44.6)	29 (46.8)	25 (42.4)		7 (22.6)	8 (72.7)	10 (58.8)	
- Female	67 (55.4)	33 (53.2)	34 (57.6)		24 (77.4)	3 (27.3)	7 (41.2)	
Age (years)	54.0 [20-83]	53.0 [20-80]	55.3 [22-83]	0.54	59.1 [22-83]	52.7 [22-72]	55.3 [30-77]	0.92
Disease characteristics:								
Disease duration (years)	19 [1-59]	17.0 [1-49]	21.0 [1-59]	0.02*	24.0 [1-59]	18.0 [6-38]	19 [11-48]	0.43
Wheelchair bound	42 (34.7)	14 (22.6)	28 (47.5)	0.04*	15 (48.3)	4 (36.4)	9 (52.9)	0.68
Ventilator dependent	40 (33.1)	17 (27.4)	23 (39.0)	0.18	14 (41.2)	3 (27.3)	6 (35.3)	0.54
Clinical tests:								
MRC sum score	82.3 [26.7-100]	84.6 [64-100]	79.2 [27-95]	0.01*	82.3 [27-95]	81.9 [61-91]	71.9 [50-92]	0.37
FVC sitting (% pred)	76.6 [9-128]	80.0 [13-118]	72.9 [9-128]	0.19	77.7 [9-121]	75.7 [22-128]	63.2 [20-119]	0.12
FVC supine (% pred) #	60.8 [19-111]	64.7 [22-111]	56.4 [19-109]	0.68	59.5 [19-109]	64.4 [28-108]	46.7 [21-106]	0.06
Postural drop (%)	28.6 [1-62]	25.7 [1-62]	31.8 [3-62]	0.41	32.9 [4-61]	25.5 [3-62]	34.2 [11-60]	0.36
Patient Reported Outcomes								
RHS	29.0 [14-36]	30 [14-36]	28.0 [16-36]	0.02*	26.4 [18-36]	29 [16-34]	29 [20-35]	0.40

Data are expressed as numbers (percentage) or as median [range]). n: number; ERT: Enzyme Replacement Therapy MRC: Medical research council (where 0= full paralysis and 5= normal strength); FVC: forced vital capacity; Postural drop: relative difference between FVC in sitting and supine position (#no FVC in supine position could be obtained in 11 patients without incontinence, in 9 with UI, 2 with FI and 3 with DI); RHS: Rotterdam Handicap Scale (where 9= unable to fulfil any, and 36= able to fulfil all applicable tasks); SF-36 PCS: Short Form 36 Physical Component Summary; MCS: Mental Component Summary (norm-based where 50 is comparable to the general population scores); FSS: Fatigue Severity scale ^(where 0= no fatigue and 7= severely fatigued). * significant at p<0.05, p-values were obtained using Pearson Chi-2 for categorical data, Mann Whitney and Kruskal-Wallis test for continuous

and for fecal incontinence 33% vs. 15%. Patients reporting any incontinence had a significantly longer disease duration than those not reporting incontinence (median 21 years (range 1-59) vs. 17 years (range 1-49) p=0.02, Table 1). They were also more affected in terms of muscle strength (MRC), functional ability (RHS), and wheelchair dependency.

Of our female patients, 79% (53 out of 67) gave birth to one or more children; 55% (29/53) of them reported incontinence. Five women (35%) reported incontinence without giving birth. There was no significant difference in maternity status between women with or without incontinence (p=0.21). Of women without incontinence 21 out of 24 (87,5%) had delivered a child via vaginal delivery and for the group with incontinence this was 27 out of 29 (93,1%). No significant difference was found between these groups (p=0.49). See table 2 for other potential risk factors for incontinence. Patients reporting UI were more commonly female (77%); while those reporting FI were frequently male (73%) (p=0.04). There were no other significant differences between patients with different types of incontinence.

Table 2 |Confounding factors for incontinence

	No incontinence	Incontinence
Vaginal delivery	21/24 (87.5%)	27/29 (93.1%)
Twin birth	-	1
Uterus extirpation	2	-
Cervix carcinoma	-	1
Ovarian carcinoma	-	1
Prostate hyperplasia	1	1

All 59 patients reporting incontinence were offered a referral to a pelvic floor physiotherapist. Of them, 41% (n=24) chose to be referred and underwent PFPT, of which 20 were contacted for an interview on their experiences (Figure 1). Two patients of 24 were excluded; one because PFPT was not continued after the intake appointment, another patient because this patient also has spina bifida, in addition to Pompe disease which may influence the reported incontinence symptoms as well. Two other patients had died. Thirty-five of the 59 patients (59%) chose not to be referred to PFPT. The main reason for non-referral was that patients indicated that the burden of incontinence was low. These patients were older, had a longer disease duration and were more often ventilator-dependent compared to those who did want to be referred (all $p<=0.02$). There were no significant differences regarding the other variables listed in table 1. We asked the physiotherapists of the 22 patients who underwent pelvic floor physiotherapy for the patients reports; we received 17.

REFERRAL TO PELVIC FLOOR PHYSIOTHERAPY (PFPT)

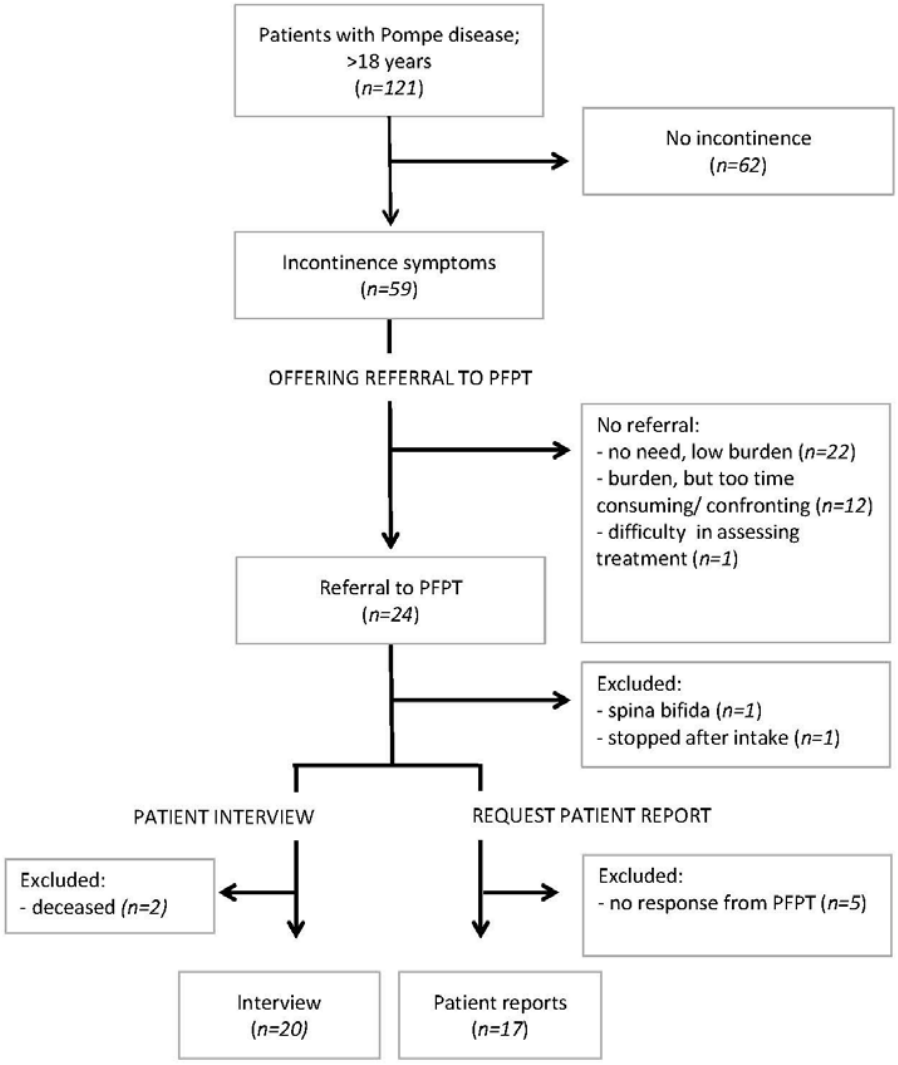

Figure 1 | Flowchart

EXPERIENCES WITH PFPT

The 17 reports of the physiotherapists revealed that the treatment interventions always comprised education and advice (e.g. on toilet behaviour, the use of incontinence material), while 94% patients received also pelvic floor muscle exercises (PFME), often in combination with myofeedback (69% of patients). The focus of the PFME appeared to differ between physiotherapists. Some focused on tonus reduction, others on improving endurance, coordination or muscle strength or a combination of those.

Before starting PFPT, all patients underwent measurements of muscle activity of the pelvic floor. Eight patients (47%) appeared to have an overactivity, while five had an underactivity, and one patient had a normal, but asymmetrical activity of the pelvic floor muscles. In three patients a combined, both over and under activity was measured.

Of the 17 patients (7 DI, 6 UI, 4 FI patients) for whom reports were received, 10 patients had completed PFPT at the time of analysis. The number of treatment sessions varied between patients with a median number of 8 (range 4-35). In two patients PFPT was still ongoing. They had completed 14 and 5 treatment sessions at the time of analysis; another patient died before ending the therapy (6 sessions). The reason of death was respiratory failure and unrelated to PFPT. Five patients had stopped PFPT after median number of 7 sessions (range 4-24). When patients were asked for what reasons that they had stopped PFPT it was either because they felt embarrassed by doing it or because of the costs of it were not being reimbursed.

After completing PFPT, activity of the pelvic floor muscles was reassessed in eight patients. The rest tone improved in all. This implied either reduction in

muscle tone when overactive or increase in muscle tone when underactive or both in patients with both under and overactive muscles in the pelvic floor region. To evaluate the effectiveness of PFPT incontinence questionnaires were used by most physiotherapists, but we also noted that there were differences in the questionnaires applied. In total 5 different questionnaires were used; for UI: PRAFAB and PSK UI; and for FI: Wexner, Vaizey and PSK FI). Before starting PFPT, 12 patients completed a questionnaire on incontinence, nine of whom completed the same questionnaires after treatment. In all patients, the scores after treatment had improved.

PATIENT INTERVIEWS

Of the 20 patients interviewed, 90% felt they benefited from therapy (median 7 on a scale from 0-10). Most often reported benefits were decreased incontinence (n=12, 60%), and increased propriocepsis of pelvic floor muscles (n=7, 35%). Eight patients (40%) reported that they were free of symptoms after therapy and seven (35%) experienced improvement of symptoms. In five patients (25%) symptoms persisted as before, although they indicated they experienced advantages from using incontinence material recommended by the physiotherapist. The elements of treatment that patients valued the most were education (n=10, 48%) and pelvic muscle exercises (PFME) in combination with myofeedback (n=11, 48%). All patients except one were satisfied with the treatment (median 8 on a scale 0-10, range 5-10), this also include the 5 patients that stopped earlier than advised by the physiotherapist.

DISCUSSION

This study shows that incontinence is common in adult patients with Pompe disease. Patients who were longer and more severely affected by the disease were more likely to report incontinence than those who were shorter and less severely affected. The majority of patients referred to pelvic floor physiotherapy, indicated they benefited from treatment.

In the Dutch general population the prevalence for UI is 0.4-18% (males) and 2.4-45% (females) [30, 31]. For Pompe disease we found higher figures of 33% in men and 46% in women. FI has been estimated to occur in 7.9% of the Dutch general population [32, 33]. Amongst our patients we found a higher prevalence both in men (33%) and in women (15%). While it is known that men have a higher prevalence of FI than women [34, 35] the high number of men with FI in our population is striking. Regarding the subtypes of incontinence gender plays a role, as it does in the general population: women more commonly experience UI, which may be related to childbirth. However, we did not find a significant difference in maternity status, neither for other risk factors for incontinence. The high frequency of vaginal deliveries reported in this study may indicate that glycogen storage did not affect the contraction function of the smooth muscles of the uterus to a large extent [36, 37].

Our study on the prevalence included 121 patients. Two other studies, including 57 and 34 patients, have investigated the prevalence in adult patients with Pompe. The studies have estimated that up to 54% suffer from UI and 20-55% of FI [8, 11]. We find comparable results, except for FI in women (15%). The range of estimates reported may be due to the use of different definitions. Both studies [8, 11], for example, reported on bowel incontinence, which besides leakage of liquid or solid stool also includes flatus. In addition, we asked about incontinence during

patients' regular visits, but anonymity by using questionnaires might be helpful in obtaining honest answers to sensitive questions [34]. Hence, our figures are likely to show only the minimum amount of patients with incontinence.

Generally, incontinence is related to a dysfunctional closure mechanism of bladder or bowel (smooth muscles) provided amongst others by the muscles of the pelvic floor(striated muscles). A lack of strength, coordination and timing issues may the underlying problem, but it can also occur that these muscles are overactive or underactive [38]. By strengthening and/or normalizing the tone and function of the pelvic floor muscles, which are striated muscles, the closure mechanism will improve. Although PFPT is commonly used in suffering from incontinence [19, 20] little attention has been paid to involvement of the pelvic musculature in Pompe disease. Surprisingly, only 41% of the patients with incontinence wished a referral for PFPT. When offered a referral to PFPT, patients did not want to take this up for several reasons. The majority indicated that the burden of incontinence was low. This is consistent with a frequently reported barrier in care-seeking behaviour in a general population with incontinence [39]. Furthermore, a part of our patients believes a referral to PFPT, combined with the regular care for Pompe disease, is too time consuming. These patients were older and more severely affected than the patients who pursued the referral. The perception of incontinence being a part of their impaired mobility, which makes it more difficult to reach the toilet in time, might play a role as well. Of note, since we pay more attention to incontinence and try to make it a topic that can be discussed at our outpatient clinic, we see more patients want to be referred to PFPT. Patients may often remain silent because of embarrassment and/or misconception that incontinence cannot be treated. Finally, physicians may add to under-treatment by not raising the topic [40, 41].

Of all patients who were referred, 90% reported that they benefited from PFPT and 75% reported a decrease of symptoms Patients' perceived improvement was corroborated by data from both physical assessments of the tone of the pelvic floor muscles and incontinence questionnaires suggest improvements after a period of PFPT. This suggests that PFPT may be beneficial to these patients. Results of the physical assessments performed by the participating physiotherapists in this study indicated a reduced function of the pelvic floor muscles before treatment; as they found overactive pelvic floor muscles in 8 out 17, at rest. It has been shown that pelvic floor muscles work in synergy with limb girdle muscles and are supposed to contract unconsciously during any increase of intra-abdominal pressure [42, 43], which occur with almost every activity from daily life. We hypothesize that, in Pompe disease, the pelvic floor muscles might be in a continuously elevated contraction to compensate for weakness of the limb-girdle muscles, to counterbalance the declining core stability. This is an overactive condition where there may be hypertonia of the pelvic floor muscles at rest, increased involuntary or voluntary contractile activity, or a decreased ability to fully relax these muscles. This will lead to early time-to-fatigue and muscle weakness, resulting in symptoms such incontinence [44].

Our study is the first to focus on PFPT as a treatment option for incontinence in Pompe disease. Still, the small number of pts, the descriptive character of the study, and the differences in methods of assessment by the physiotherapists, prohibit any statements on the effectiveness of specific interventions or parts of it, and about which intervention fits best. Multiple factors might have contributed to the effects that were measured. The reported benefit might also result from the attention paid to shameful symptoms and aids offered, such as incontinence material. However, as assessment and correction of the pelvic floor muscle activation is argued to be an essential part of effective PFMT it is also plausible

that the efficacy of treatment might depend on the striated muscle that have been trained.

Nevertheless, some recommendations can be made. Given the high prevalence of incontinence in this population clinicians should routinely ask about incontinence. In order to be able to interpret the severity and implications for everyday practice, uniform, reliable and valid incontinence questionnaires should be used. In addition, patients could be advised to start PFPT considering its suggested results in this study. However ,more research with a prospective design with standardized outcome measures and interventions, is needed to better understand benefits, most effective trainings regiment and barriers to patients adherence. In addition, future direction should also be taken to unravel the pathophysiology, in order to see to what extend smooth muscles, striated muscles and neurological innervation play a role in incontinence in Pompe disease. With special interest in the role and condition of the pelvic floor muscles during activities from daily life.

CONCLUSION

This study has shown a prevalence of incontinence in adult Pompe patients of nearly 50%. Compared to patients not reporting incontinence, these patients are longer and more severely affected by Pompe disease. Pelvic floor physiotherapy aimed at normalizing the tonus of the pelvic floor musculature may be a useful therapy for these patients. Patients who were treated by PFPT reported a decrease of symptoms and perceived the treatment as beneficial and physical assessments and incontinence questionnaires suggested improvements after treatment. More standardized prospective studies are needed to assess if PFPT is a useful treatment in this patient group.

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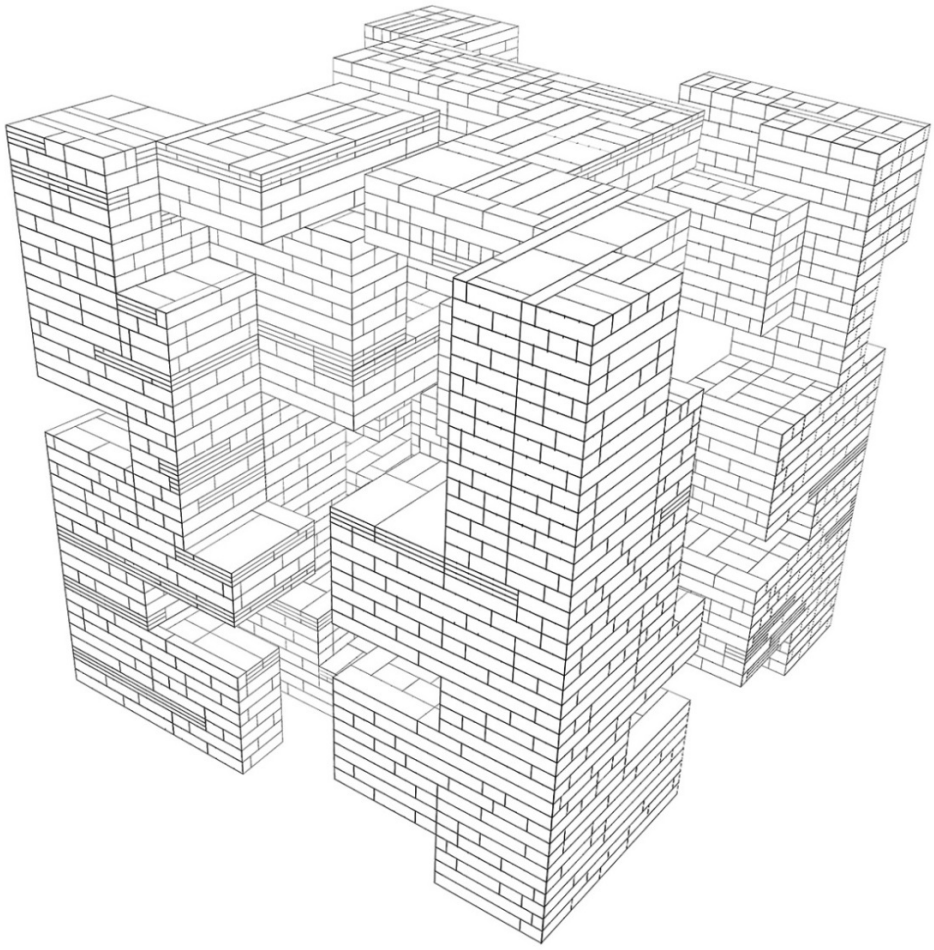

CHAPTER 07

GENERAL DISCUSSION

DISCUSSION

With the introduction of enzyme replacement therapy in 2006, Pompe disease became the first neuromuscular disorder for which a disease-specific treatment is available. This changed the perspectives of patients with Pompe disease for the better. With these changed perspectives the call for additional forms of therapy, such as physiotherapy, became stronger.

The overall aim of this thesis was to describe the role of the physiotherapy in the field of Pompe disease and to investigate whether physiotherapeutic care of patients with Pompe disease is a valuable addition to the existing enzyme replacement therapy. For this we identified specific sub-aims:

1. to gain insight into the existing generic physiotherapeutic care in Pompe;
2. to explore the feasibility and effectiveness of a training intervention;
3. to gain insight into the extent to which walking performance can be explained by muscle strength and other mediating factors with the aim of building a model;
4. to determine the prevalence of incontinence in the Dutch Pompe population and to explore the application of pelvic floor physiotherapy.

This chapter discusses the main findings of our studies and their significance for clinical practice. Besides it describes the role of the physiotherapist in Pompe disease in specialised centres, including physiotherapeutic testing, and it also provides perspectives for the future.

MAIN CONCLUSIONS OF THIS THESIS

- There is a lack of guidance for physiotherapeutic care of patients with Pompe disease and a strong need for it (chapter 2)
- Reduced muscle strength of the lower extremities, higher BMI, male gender, use of respiratory support and older age increase the risk for decreased walking performance (Chapter 5).
- A combined training program, consisting of aerobic, strength and core stability training appears to be safe and improves endurance, core balance, muscle strength and muscle function, and reduces fatigue and pain (Chapter 3 & 4).
- One in two adult patients with Pompe disease have incontinence.
- Both regular and pelvic floor physiotherapeutic care of patients with Pompe disease in the Netherlands is scattered and diverse (chapter 2 & 6).
- When offered pelvic floor physiotherapy for incontinence, 41% chose to be referred, of which 75% benefited. (Chapter 6)

MAIN FINDINGS

PHYSIOTHERAPEUTIC CARE OF PATIENTS WITH POMPE DISEASE IN THE NETHERLANDS

PHYSIOTHERAPY IN THE FIRST LINE

Before the introduction of enzyme replacement therapy (ERT) a sedentary lifestyle was recommended to patients with Pompe disease to prevent overuse of the damaged muscle tissue [1]. This may be one of the reasons, together with the rarity of the disease, that little was known about -the effectiveness of- physiotherapy in Pompe disease in general and exercise in particular. With the success of ERT, perspectives of patients changed and the call for additional forms of therapy, such as physiotherapy, became stronger. In order to get an insight into current practices in terms of referral, type of treatment, and perceived benefit, we performed a survey among 88 Dutch adult Pompe patients and 31 physiotherapists.

At the time of this survey (2009) more than half of the patients did not receive physiotherapeutic care for symptoms related to Pompe disease and 40% of patients had never been treated by a physiotherapist. The most common reason for not being seen by a physiotherapist was that patients indicated that they perceived no restrictions in daily life. We noticed the same in the study on incontinence. When offered a referral to pelvic floor physiotherapy, 59% of the patients with reported incontinence did not want to take this up, mainly because they stated that they perceived relatively little burden of incontinence. This is consistent with a study on care-seeking behaviour in a general population, for which 1,067 Dutch people have been questioned on the use of physiotherapy.

More than half of the people with physical complaints procrastinated a visit to a physiotherapist, or did not visit at all [2]. One of the reasons for this procrastination behaviour was denial of physical complaints. Also, a lack of knowledge about the referral procedure (in the Netherlands the physiotherapist can be accessed directly without a referral) and treatment possibilities and the costs of physiotherapeutic care may play a role [3].

In our study on existing physiotherapeutic care in Pompe disease, decreased muscle strength and loss of general condition were the main reasons for referral by medical doctors. These reasons for referral were largely reflected in both treatment goals and interventions used, but in 32% of cases a discrepancy was observed between treatment goals and reason for referral, and in 47% of cases the treatment given did not match the reason for referral. Although there was a wide range of treatment interventions, the most commonly used intervention was muscle strengthening exercises, often combined with aerobic exercises. However, there was a lot of uncertainty about the way the treatment should be designed, in particular, about the extent of muscle load-bearing capacity that patients could tolerate. This can be partly explained by the rarity of Pompe disease, which gives the physiotherapist little chance to develop relevant experience with this disease. Also the lack of guidance and research leads to unclearness on the extent of capacity that patients can tolerate. The possible added value of physiotherapeutic care in patients with Pompe disease could not be evaluated due to the wide range of reported treatment interventions and the large variety of outcome measures used. To examine the added value of physiotherapy in Pompe disease, there must be uniformity with regard to treatment interventions. Both patients and physiotherapists indicated in the survey that they had a strong need for clear guidelines for physiotherapeutic care in Pompe disease in general and exercise therapy in particular.

EXERCISE TRAINING IN MILDLY AFFECTED PATIENTS WITH POMPE DISEASE

A first step in the development of physiotherapeutic guidelines was the elaboration of a standardized and well-structured exercise program. In related neuromuscular diseases, exercise training has been reported to beneficial effects on both endurance and muscle strength [4-8]. Before ERT became available, one study had been conducted on exercise training in patients with Pompe disease [9]. Over a mean period of 4,5 years, 26 patients were subjected to a combination of a diet and submaximal aerobic exercises, which was reported to lead to a slower deterioration of muscle function. After the introduction of ERT, another study reported on the positive effect of a 20-week exercise program consisting of aerobic and progressive resistance exercises, in combination with ERT in 5 patients. This small study showed an improvement on both muscle strength and walking distance [10]. These preliminary data strengthened our ideas that the exercise training program that we had introduced as part of a study could be an effective way to increase strength and endurance in adult patients with Pompe disease. So far, due to the small numbers of patients and the diverse interventions and outcome measures used, firm conclusions about the effectiveness of these interventions cannot be drawn.

Before starting a study on the safety and efficacy of exercise training in 25 patients we carefully considered which exercises to include. Besides cardio exercises, we also chose to train all those muscle groups that are affected by Pompe disease, including the core muscles. This led to a three month intervention study in which we offered a combined program of aerobic, strength and core stability training. The study showed that this combined program was safe and

improved endurance, muscle strength and core stability. Our study also showed that such a comprehensive exercise intervention program also has a positive effect on fatigue and pain scores and may improve mental health. The assumption that exercises can cause structural damage to muscle cells with no or less GAA activity, thereby aggravating muscle weakness, is not confirmed by our findings. Moreover, the results of our study imply that muscles affected by Pompe disease are indeed trainable, with regard strength, endurance and proprioception. However, we are not certain whether the increased strength resulted from strength training, core stability training or from both. Core stability may support gains in muscle strength by improving proprioception and coordination.

CORE STABILITY

The core region is the area bounded anteriorly by the abdominal muscles, posteriorly by the lumbar multifidus, superiorly by the diaphragm, and inferiorly by the pelvic floor muscles (PFM) [11]. These muscles are important for stabilizing the spine and pelvis, providing proximal stability for distal mobility and function of the limbs during everyday activities. It has been theorized that a strong core will allow a transfer of forces from the lower extremities to the upper body with a minimal dissipation of energy in the trunk. If power is created but not transferred, performance (i.e., running, jumping, throwing, etc.) will be negatively affected [12]. The sequence of muscle activation during whole body movements was examined in two studies and it was found that some of the core stabilizers (i.e., mm. Transversus abdominis, Multifidus, Rectus abdominis, and Oblique abdominals) were consistently activated before any limb movements [13, 14]. It is the mm. Multifidus and the Obliquus Internus Abdominis that are affected first, followed by the Transversus and Rectus Abdominis muscles, according to a MRI study in 30 patients with Pompe disease [15]. The core stability exercises applied

in our training study, in prone, supine and side positions, target these muscle groups. Several studies examined core muscle recruitment while performing these so-called bridge exercises [16, 17]. Depending on the individual needs of a patients some of the exercises may be more beneficial than others to achieve strength. However all exercises demonstrate co-activation of muscle groups and should therefore be beneficial for stabilization or endurance training [17]. It is however not clear whether the change in balance control can be transferred into everyday life [18]. Although the distance walked, measured by the 6 MWT, and speed of movement, measured by the four step climb, improved after training, the program did not improve the other motor function parameters, either self-reported (R-PAct and PCS) or clinically observed (QMFT). Moreover, we did not find significant correlations between core stability and any of the motor function parameters. A possible explanation is that the core assessment was an isometric muscle endurance test, whereas the motor function tests, as used in this study, involved dynamic movement. Okada et al. advocate that the lack of correlation between core stability and motor function suggest that core stability alone is not a strong predictor of performance [13]. Our combined training program thus seems to have a positive effect on the speed of movement, but not on the quality of motor function, i.e. how these activities are performed. It is unlikely that an improvement in speed without improvement in the way these movements are executed is clinically useful for patients. It is nevertheless also possible that the period of 12 weeks may be too short to achieve changes in the quality of motor function.

RECOMMENDATIONS FOR MORE SEVERELY AFFECTED PATIENTS WITH POMPE DISEASE

Mildly affected patients respond well to the specific training program, consisting of a combination of strength, endurance and core stability exercises. Patients followed this training program for three times a week. Although the compliance was high, due to supervision and weekly telephone consultations, a training frequency of three times a week is rather time consuming. Moreover, too many exercises may not be feasible for patients due to commonly reported exercise barriers such as lack of time and fatigue [19]. All patients, except two, continued this training program two times a week after the end of the study. This reflects the beneficial effects these patients experienced. These positive experiences make it worthwhile to adapt the program for more severely affected patients. Adaptations involve modifications in length or intensity of each of the different parts of the program and/or modifications of the equipment. Arm crank ergometers and wheelchair ergometers are the instruments most commonly used to train endurance of wheelchair-dependent patients. For the core stability training a Swiss ball or balance cushion can be used. When the minimum weight of the traditional fitness equipment is still too high to train the patients, elastic straps, can be used to perform each exercise from our study. We have developed a folder containing all these exercises. Finally, if some of the exercises from our initially training study are too strenuous, they can be replaced by exercises that target the muscle groups that are still trainable and are important for performing daily activities independently, such as eating and drinking or personal hygiene.

If rehabilitation goals remain limited to improve outcomes on body structure & function level of the ICF model (see figure 1, page 17, general introduction), this will reduce the ability of helping patients to improve activities from daily life. The results of our training study therefore support specificity of training. Task-specific

training complementary to exercise therapy have shown to have added value in post stroke patients [20]. Task-specific strength training combines both the concepts of strength training and task-specific training. Strength training can be defined as the progressive increase in resistance to a muscle or movement during training to induce greater ability to produce and sustain force. Task-specific training can be defined as motor learning enhancing specificity of training by involving practice of activities that are specific to the intended activity [21].

WALKING PERFORMANCE

Walking, climbing stairs, lifting and bending are every day functional activities that are frequently limited in patients with Pompe disease. Hagemans et al. reported that 87% of patients with Pompe disease who were not receiving ERT, experienced problems with walking, varying from imbalance or a waddling gait to a complete inability to walk [22]. The loss of the ability to walk is one of the most prominent signs and debilitating effects of the disease and has been shown to be an important factor in determining patients' quality of life. In general, retaining the ability to walk is important to maintain independent from caregivers [23-25].

The relation between muscle strength and walking has been well established in healthy individuals and also in (related) neuromuscular disorders [26-28]. However, for Pompe disease this relation was not clear yet. Understanding relative contributions of lower extremity muscle strength to walking performance might help to tailor physiotherapeutic interventions. As strength training is one of the three pillars of our exercise protocol for patients with Pompe disease, it might, in this light, be important to prioritize strength training targets. Therefore, we studied the associations of walking performance with muscle strength in four specific lower extremity muscle groups in 107 adult patients with Pompe disease. Walking performance declined most obviously with decreasing strength of the hip

flexion and abduction. The strength of knee extension only varied significantly between walking with aids and unable to walk. Knee flexion did not distinguish between any of the four consecutive categories. Of note, the results of this study do not suggest that interventions should exclusively target hip abduction and flexion, and knee extension. It is also important to consider the complexity and timing of muscle activation during walking [29]. Concerted contraction of muscle groups as a compensation for weakness may also play a role. In addition, other risk factors, both demographic and disease specific characteristics, might contribute to a reduced walking performance as well. For that reason we developed a multivariate regression model to describe walking performance. Besides reduced muscle strength, a higher BMI, older age, male gender and the use of a ventilator increased the patient's risk on the inability to walk. Like strength, BMI is a factor modifiable by lifestyle changes and therefore a potential target for intervention.

For clinical use, the regression model was transformed into a nomogram. Although a patient's actual walking performance can be observed, this nomogram can be helpful in the physiotherapeutic management of patients with Pompe disease. The nomogram allows the visualization of the chances on a particular walking category of a patient, which can be used for counselling purposes such as discussing the use of (walking) aids, life style changes and exercises. By using the nomogram, the discrepancies between performance and capacity can also be made transparent; whether a patient—based on risk factors—is capable of more or less than what a patient shows in terms of walking performance. Both could lead to conditions that are undesirable, whereby intervention by a therapist is needed. Underload might be related to a decreased activity level, which could result in disuse atrophy. Overload might be associated with a higher risk of falling.

The current model is based on cross-sectional data which do not predict future changes. To develop a prediction model repeated measurements over time are needed. Besides, future studies are needed to verify whether other muscle groups, known to be associated with gait performance and/or frequently involved in Pompe disease, might be included as well. It is known that weakness of hip extensors and core stabilizers also affect the walking performance [12] [29].

INCONTINENCE IN POMPE DISEASE

The pattern of muscle weakness in Pompe disease typically fits a pattern of limb-girdle myopathy, with the core and hip muscles being the most affected muscle groups [30-32]. Caudal, the core region is bounded by the pelvic floor (figure 1) [11]. Although the pelvic floor muscles (PFM) are part of the limb-girdle region, possible involvement of this muscle group and the accompanying consequences have remained underexposed in Pompe disease. The PFM are part of the core stability mechanism and their function is interdependent with other muscles of this system [33]. Pelvic floor muscles contribute to trunk and lower extremity movement control by generating and controlling intra-abdominal pressure together with other muscles surrounding the abdominal cavity [14, 33, 34]. PFM are also likely to be active with respiratory tasks. It is well accepted that PFM activity accompanies coughing and resisted expiration [34, 35]. Therewithal, PFM also contribute to continence. Continence is achieved when the pressure resulting from direct action of the PFM is greater than the pressure exerted on the bladder through abdominal Valsalva-forceful attempted exhalation against a closed airway, which enhanced the abdominal pressure- or bladder smooth muscle contraction [36].

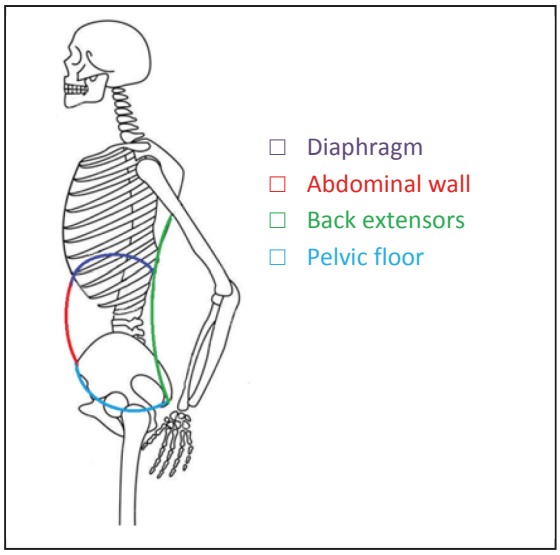

Figure 1 | Muscles of the core

A handful of studies report on the occurrence of incontinence in adult patients with Pompe disease, considering glycogen accumulation in smooth muscle tissue of both bladder and bowel as main cause [37-41]. In a general population incontinence is related to a dysfunctional closing mechanism of bladder, sphincter or PFM. Pathophysiologic hypotheses for incontinence in myopathies, such as myotonic dystrophy, include additional striated pelvic floor muscle involvement [42]. This is underlined by a MRI study in adults with Pompe disease showing that PFM are also affected [15]. The involvement of the muscles of the pelvic floor may lead to pelvic floor dysfunction, defined as abnormal function of the pelvic floor muscles and structures that depend on its support [43]. Dysfunction of the pelvic floor muscle can cause imbalances of the pelvic floor muscles and abdominal pressure that result in urinary (UI) and fecal incontinence (FI) [44].

Over the years, a substantial number of patients indicated that they experienced incontinence during daily life activities and reported this at their regular visits to our centre. Besides our study, three studies have reported on the prevalence of

incontinence in adult patients, albeit using different definitions resulting in a wide range of figures [37, 38, 40]. To get a clear picture of the prevalence in our population we started asking about incontinence during patients' regular visits. In addition, we offered patients with incontinence a referral to a pelvic floor physiotherapist as they are educated in treating pelvic floor dysfunction. Although, pelvic floor physiotherapy (PFPT) might be beneficial, it still is an unknown treatment option for patients with Pompe disease. Therefore, we initiated a study aiming to describe the characteristics of incontinent patients with Pompe disease on one hand and to describe the referral to PFPT as a potential beneficial treatment option for this population on the other.

The first results of this study focused on the prevalence of incontinence in the Dutch Pompe population and their characteristics. We found a prevalence of incontinence in about one in two adult patients. Patients who were longer and more severely affected by the disease were more likely to report incontinence than those who were shorter and less severely affected. It is striking that, in contrast to a general population, there is no association between incontinence and age. Consequently, incontinence symptoms can occur at any age, which is in line with two studies on incontinence in Pompe disease [38, 40]. Our prevalence figures appeared in the same range as compared to the general population in the Netherlands. When we initiated this study, we expected a significantly higher incidence of incontinence in patients with Pompe compared to the general population. However, we distinguish double incontinence (DI) as a separate category of incontinence. This means that our prevalence figures for both UI and FI were relatively lower, making these data incomparable. When assuming two categories UI and FI we find, compared to the general population, a slightly higher prevalence for UI in Pompe patients (39.7% versus 36.8%), and a substantial higher prevalence FI (23% versus 7.9%), with a preponderance of FI in men as

opposed to women. Other studies reporting the prevalence of incontinence in adult patients with Pompe do not distinguish either between UI, FI and DI. In addition, the use of different definitions and outcome measures make these data incomparable. Finally, since incontinence is still a topic which is often associated with embarrassment, the anonymous survey make patients admit their problems more frequently and honestly [45]. Incontinence is often unreported by patients and undetected by physicians, and consequently the actual prevalence may be higher[46].

The second part of this study described the referral to pelvic floor physiotherapy (PFPT) and the characteristics and reported outcomes of treatment. In a general population PFPT is an evidence based and minimally invasive therapy, and may be offered as a first-line treatment choice to patients experiencing pelvic floor dysfunction. PFPT was offered to all patients reporting incontinence. However, almost two-thirds chose not to be referred. When offering a referral, more than half of our patients (59%) did not want to take this up, because they perceived relatively little burden of incontinence (60%) in daily life. This is also seen in a general population, as incontinence may not be seen as life threatening and patients therefore only seek help when the symptoms become disabling or bothersome [47]. Also in our survey on general physiotherapeutic practice in the Netherlands little symptom burden was the main reason for patients not wanting to be referred. It can be questioned whether there is actually little symptom burden or that a lack of knowledge among patients about physiotherapeutic care in neuromuscular diseases might contribute as well. Nowadays, the majority of our Pompe population receives physiotherapeutic care for symptoms related to Pompe disease. This is partly due to information about the usefulness of physiotherapy, which are based on the results of our training study.

Another resemblance between these studies is the diversity of interventions, e.g. types of exercise used, quantity, intensity and subjectivity and variability of outcome measures used. This is a common problem in evaluating and comparing results of physiotherapeutic interventions in neuromuscular diseases [25]. The underlying problem is the heterogeneity of the patient population due to the difference in the specific progress of the disease and in the severity of the muscle involvement, which causes variations in muscle response to exercise. Also patient specific characteristics play a role, such as pre-exercise conditioning status and motivation to carry out a rehabilitation program. [22].

Although the majority of the patients who received PFPT perceived it as beneficial, it was not possible to assess how this corresponded with changes in outcomes such as tone, strength or endurance of the pelvic floor muscles. Consequently, there is no consensus regarding the most efficient intervention or combination of pelvic floor physiotherapy interventions for Pompe disease. Therefore, future studies are needed with a core set of outcome measures and standardised interventions. First of all, the pelvic floor muscle function has to be investigated. It remains unclear whether there is overactivity, underactivity of the pelvic floor muscles or a combination of both, and to what extent. The assessment of muscle tone, strength, endurance and coordination is difficult due to uniform use of reliable measurement techniques, and absence of cut-off values for pathological conditions [36]. Future direction should also be taken to unravel the pathophysiology, in order to see to what extent smooth muscles, striated muscles and neurological innervation play a role in incontinence in Pompe disease. The exact pathophysiological pathways leading to incontinence in Pompe disease are still unknown. The most reliable hypothesis suggests that accumulation of glycogen in both smooth and striated musculature is causative, and the possible involvement of the autonomic nervous system as well. This could allow better

tailoring of individual training programmes and would enable more Pompe patients with incontinence to benefit from PFPT.

PHYSIOTHERAPY IN SPECIALIZED CENTRES

All patients in the Netherlands with a confirmed diagnosis of Pompe disease visit the Center for Lysosomal and Metabolic Diseases (CLMD), Erasmus MC University Medical Center in Rotterdam regularly. This centre is the Dutch national referral centre for patients with Pompe disease. Once the diagnosis has been made, physiotherapeutic testing plays an important role in monitoring the disease progression and estimating the effectiveness of treatment by identifying and quantifying muscle involvement and motor and functional impairment.

MUSCLE STRENGTH TESTING

Skeletal muscle strength can be measured with either manual muscle testing (MMT) or quantitative muscle testing (QMT). The most commonly used method to evaluate manual muscle strength is the Medical Research Council Manual Muscle Testing scale (MRC). This method involves testing key muscles from the upper and lower extremities against gravity and the examiner's resistance and grading the patient's strength on a 0 to 5 scale [48]. MMT is a quick, simple to perform and an inexpensive way to measure the distribution and progression of weakness in specific muscle groups and can be performed with acceptable inter-rater reliability by trained health care providers in any setting [49]. However, the outcome is subjective, and the scaling does not meet the requirements of an interval scale, where grade '4' may encompass a span of weakness so large that clinically relevant details are lost [50, 51].

QMT involves the use of hand-held or fixed dynamometers. Dynamometry and fixed (computerized) QMT involve maximum voluntary isometric contraction against an electronic force transducer or strain gauge [52]. Both types of muscle tests provide quantitative data on a continuous scale and show fair to good reliability. The choice between the different muscle tests depends on both the availability of the equipment, training of the examiner and the applicability in the patients. A hand-held dynamometer (HHD) and a fixed dynamometer yield comparable results in patients with neuromuscular disease. However, the use of an HHD depends on stabilization by the tester, creating a potential source of tester error, mainly when stronger muscles are being tested (ie, those producing forces >250 N) [52]. Compared to a hand-held device, fixed QMT require sophisticated equipment which makes it more expensive. Moreover, fixed QMT is limited by its applicability. More severely affected patients experience difficulties or limitations in accessing the test couch or chair. The number of muscles that can be tested is less and a room with a fixed set-up of the equipment is needed. In contrast, HHD can be used at whatever location. A limitation of all muscle tests is the lack of a gold standard method for measuring strength of the trunk muscles [53].

Table 1 | Overview of different types of muscle strength testing / different tools for isolated muscle strength testing

	MMT		QMT
	MRC	HHD	Fixed dynamometry
Objective outcomes:	-	+	+
- Reliable outcomes, strength <250N	N/A	+	+
- Reliable outcomes, strength >250N		-	+
- Reproducible outcomes	N/A	+	+
Easy to perform	+	+	-
Suitable to all patients	+	+	-
Applicable for all muscles	+	+	-
Price devices	N/A	+	-

MUSCLE FUNCTION TESTING

Functional measures are recommended to evaluate the strength, function and endurance of the motor system as a whole. These measures assess typical gross motor tasks and antigravity functional movements with standardized methods including timed functional tests. Functional measures can assist in monitoring disease progression and response to treatment. Muscle function can be measured using a variety of tests. The 6 minute walk test (6MWT) is a frequently used test in the evaluation of walking capacity and provides information on endurance as well as walking speed [54]. A downside of this test is that it is not suitable for (partially) wheelchair bound patients. Four other timed tests are often used both at regular assessments and in trials in Pompe disease, because they reflect aspects relevant in daily life: walking 10 metres, climbing four steps, standing up from supine position and standing up from a chair. Besides timed tests, which measure the speed of movement, also the quantitative motor function test (QMFT), which measures the quality of movement, is frequently used. This test specifically designed and validated for Pompe patients and consists of 16 specific motor skills related to daily activities and to activities that are difficult to execute for patients with Pompe disease [55]. All aforementioned functional measures refer to the capacity qualifier of the ICF model (see figure 2) which describes the ability to execute a motor task or action indicating the highest probable level of functioning. It should be noted that these outcomes, measured in a standardized environment, may differ from daily practice, which referrers to the performance qualifier of the ICF model [56, 57].

Performance in daily life can be measured using objective tools (accelerometers) and subjective (questionnaires) [58]. An accelerometer provides objective measures in daily life of the amount of physical activity patients engage in. A frequently used tool in Pompe disease to assess motor function in daily life is the

Rasch-built Pompe-specific Activity Scale (R-PAct). This questionnaire encompasses 18 activities of daily living reported to be the most important and limiting activities and social participation throughout the entire disease spectrum in patients with Pompe disease [59]. By using the Rotterdam Handicap scale (RHS) insight into the social consequences of Pompe disease can be obtained [60, 61]. This scale comprises nine inquiries (mobility indoors, mobility outdoors, kitchen tasks, domestic tasks indoors, domestic tasks outdoors, leisure activities indoors, leisure activities outdoors, ability to drive a car/go by bus/ride a bicycle, and ability to work/study) [62].

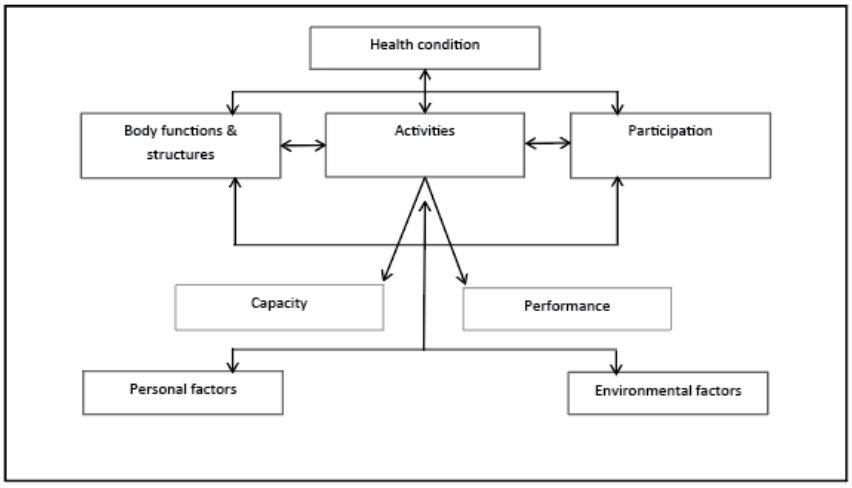

Figure 2 | ICF levels and subdivision

Respiratory assessments

In some experts centres for Pompe disease physiotherapists are involved in pulmonary function testing. The most common respiratory symptoms in Pompe disease are shortness of breath with exercise and decreased respiratory function in supine versus upright positions, both resulting from diaphragmatic muscle weakness [63]. Pulmonary function testing involves forced vital capacity (FVC) in sitting and supine positions, and maximal inspiratory and expiratory pressure (MIP and MEP). As diaphragmatic weakness is common in Pompe disease [64] it is important to measure the FVC in both positions. Both mouth pressure measurements provide information on respiratory muscle strength [65]. Pulmonary testing often encompasses peak cough flow (PCF) and/or voluntary cough peak expiratory flow (PEF).

Fatigue assessment

Fatigue is a commonly reported problem in Pompe patients [66] and it leads to decreased ability to sustain voluntary physical and mental activities. The fatigue severity scale (FSS) is a generic nine-item questionnaire that evaluates the severity and impact of fatigue [67]. No disease-specific equivalent exists for Pompe patients.

RECOMMENDATIONS

The systematic use of standardized measures in each category of the ICF model is recommended for monitoring disease process over time. Appropriate assessments and interpretation of results enable individualized monitoring of the disease progress and adjustment of treatment exercise programs to safely optimize the patient's strength, endurance and motor function. In 2014 an agreement was reached on a minimal dataset of outcome measures between nine European countries, for both data sharing purposes and as a recommendation for use in monitoring patients' response to treatment [4]. All clinical assessments selected were commonly used in the participating countries and deemed to be relatively simple to use. With regard to the clinical domains, this dataset covers skeletal muscle strength and function and pulmonary function. This set encompasses the MRC, 6 MWT, timed tests (ie. walking 10 metres, climbing four steps, standing up from supine position and standing up from a chair) and pulmonary function tests. Given the benefits of HHD, skeletal muscle strength should be added to the MMT, examining muscle groups specially affected in Pompe disease.

Since pain is frequently reported in Pompe disease [60, 68, 69], assessment of pain is required at every patient encounter. Pain may be isolated or generalized and may be exacerbated by fatigue, overactivity and exercise. As no disease specific pain questionnaire is available, the subscale bodily pain of the SF-36 is used to evaluate pain in Pompe disease [68, 69] and the use of a generic pain assessment tool such as the visual analogue scale (VAS) might be appropriate. Besides, the physiotherapist should also exam the possible underlying musculoskeletal complaints of the shoulder, hip or low back pain and symptoms secondary to Pompe disease, such as restricted range of motion.

In addition, given the high prevalence of incontinence of nearly one in two, reported in this thesis, clinicians should routinely ask about symptoms of incontinence. In order to be able to interpret the severity and implications for everyday practice, reliable and valid incontinence questionnaires such as the PRAFAB for urine incontinence [70] and Wexner for fecal incontinence should be used.

Finally, with regard to outcome measures, an intermediary role is reserved for physiotherapists specialized centres, where many patients with Pompe disease are seen. The physiotherapist in a such a centre may identify the need for additional physiotherapy treatment and adaptive equipment on the basis of the outcome measures used. Results of the described assessments should therefore also be used for referral to physiotherapists in the first line. The nomogram, described in this thesis, can be used in addition to the clinical assessments in the referral to the physiotherapists in the first line. The nomogram can, besides its use in monitoring the patient's response to treatment, also be used for evaluation of physiotherapeutic interventions. In this way, the wide variety of outcome measures can be reduced, whereby the presumed added value of physiotherapy can be evaluated unambiguously.

RESPIRATORY MUSCLE TRAINING

Although ERT has positive effects on skeletal muscle function, the effects on lung function especially in supine position seem to be less pronounced [71, 72]. In two MRI studies on respiratory dysfunction in Pompe disease, severe dysfunction of the diaphragm was observed [63, 73]. Dysfunction of the diaphragm and weakness of respiratory muscles is considered to play an important role in respiratory failure, the main cause of death in Pompe disease. Theoretically, respiratory muscles are morphologically skeletal muscles and should respond to

repeated training similar to any other locomotor muscles [74]. Therefore, training of these muscles might be a treatment option in Pompe disease. Respiratory muscle training (RMT), including inspiratory and expiratory muscle training, is a well-known and established treatment in patients with chronic obstructive lung disease [75], neurodegenerative diseases, like multiple sclerosis and lateral amyotrophic sclerosis [76] and several neuromuscular disorders [77] such as Duchenne muscular dystrophy [78, 79]. The principle of inspiratory muscle training is to improve the strength of the diaphragm and the external intercostal muscles [75]. Evidence shows that improvement of inspiratory muscle strength might be related to decreased effort in breathing and a positive change in the experience of dyspnoea [75]. Little is known about the effect of RMT on pulmonary function in patients with Pompe disease. The existing studies on RMT in Pompe disease [74, 80, 81] lack comparability due to different training programs. Two out of three applied IMT, the other RMT, with varying baseline intensity, increase of intensity and length of the training period. All studies showed an increased maximum inspiratory pressure (MIP). However, no effect on spirometry (e.g. forced vital capacity), motor function tests or patients reported outcome measures was observed. This might be due to small sample sizes. This could also be due to the fact that in 2 out of 3 studies only inspiratory muscle strength was trained. In many cases it is cough insufficiency (in which expiratory muscle strength plays a role) that causes morbidity and mortality in patients with neuromuscular diseases [82]. Furthermore, the type of training, in which the main aim is to enhance the respiratory muscle strength, might lead to the absence of effects on other than muscle strength related outcome measures. A more clinically meaningful improvement might be expected when combining it with respiratory endurance training [74]. This is something that should be further explored in the future. Larger sample randomised controlled trials are needed to

determine efficacy of RMT, targeting both strength and endurance, in patients with Pompe disease.

In conclusion, the role of the physiotherapist in the follow-up, treatment and guidance of Pompe patients is broad. The studies presented in this thesis were instrumental to structure and improve the standardized follow-up and treatment programs for patients. We may also conclude that the role of physiotherapist does not end here and that there are important challenges ahead of us that may help to further improve the prospects and fulfil the unmet needs of patients.

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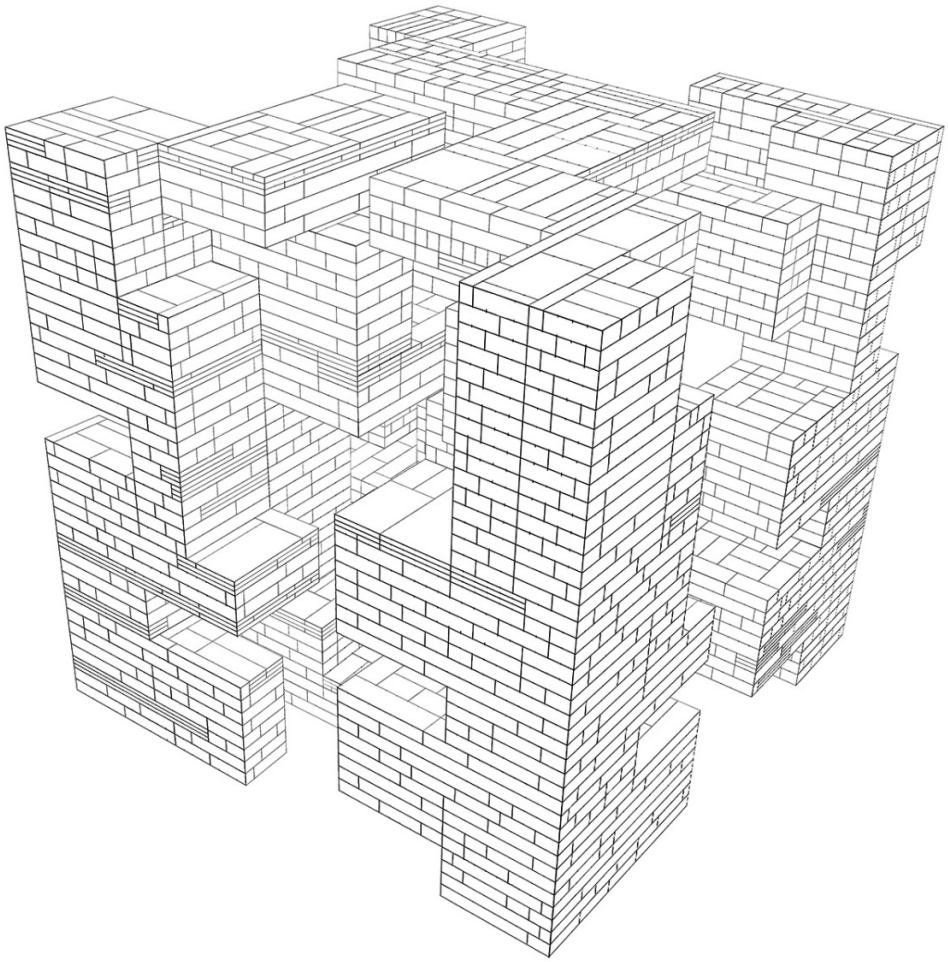

ADDENDUM

SUMMARY

Pompe disease is a rare inheritable metabolic myopathy and lysosomal storage disorder. It is caused by deficiency of the lysosomal enzyme acid alpha-glucosidase, which is needed to break down glycogen in the lysosomes. As a result of this deficiency, glycogen accumulates in several tissues, especially muscle. This leads to the loss of muscle strength and function, ultimately leading to wheelchair and ventilator dependency.

In 2006, enzyme replacement therapy (ERT) was registered for all patients with Pompe disease, changing patients' perspectives in terms of improved survival, increased muscle strength and walking distance and stabilisation of pulmonary function. However, not all patients respond equally well, and not all muscle damage and functional impairment can be resolved. Therefore it remains important to find additional ways to keep the physical function of these patients as good as possible. Physiotherapy aims to maximize the benefits of enzyme replacement and to promote and maintain the maximum level of function, functional independence, and participation. However, guidelines for physiotherapeutic care are not established for Pompe disease.

This thesis aimed to investigate whether physiotherapeutic care of patients with Pompe disease can be a valuable addition to the existing ERT and how this care can be organised. The studies included in this thesis explore the referral patterns to contemporary physiotherapeutic care and their content (both regular physiotherapy and pelvic floor physiotherapy), the use of exercise training to improve patients' functioning (beyond any improvements obtained from ERT), as well as risk factors influencing patients' walking performance.

Chapter 1 provides a general introduction to Pompe disease and physiotherapeutic care. It provides background information about disease pathogenesis, clinical presentation and physiotherapeutic care in neuromuscular diseases.

An overview of the contemporary physiotherapy practice in the Netherlands is given in **Chapter 2**. A survey of 88 adult patients with Pompe disease and 31 PTs was performed. Less than 60% of the patients had ever received physiotherapeutic care for symptoms related to Pompe disease. At time of the survey less than 40% was under treatment of a physiotherapist. Our study showed that treatment objectives and interventions were often not in line with the referral reason and that the applied treatment interventions were diverse and scattered. Nevertheless, the majority of patients and physiotherapists perceived physiotherapy as beneficial. It was concluded that there was a great need for guidelines for physiotherapeutic care to harmonize the approaches.

In **chapter 3** and **4** we studied the safety, feasibility and added value of exercise training in addition to ERT. During 12 weeks 25 patients followed a combined exercise program, consisting of aerobic, resistance and core stability exercises three times a week. In **chapter 3** we evaluated the effects this exercise program on endurance, muscle strength and muscle function and core stability, while **chapter 4** focussed on pain, fatigue, physical and mental functioning. 23 of the patients successfully completed the training. We showed that the training program is feasible and was not associated with adverse effects. Furthermore, the training helps to improve endurance, muscle strength, muscle function and core stability. The training program improved signs of fatigue and pain and tended to improve mental health. These results showed that exercise training can be performed safely in patients who are mildly affected with Pompe disease, and seems to offer added value for these patients.

The loss of the ability to walk normally is one of the most prominent signs Pompe disease, and has been shown to impact greatly on patients' quality of life. Therefore, in the treatment of these patients, the preservation of the remaining level of walking performance is of great importance. In **chapter 5** we explored factors that may influence walking performance in adult patients with Pompe disease, with focus on the role of muscle strength of four muscle groups of the lower extremity. Based on 107 patients, we found that walking performance could be explained by age, gender, BMI, the use of ventilator support and muscle strength of hip abductors and knee extensors. Based on this a nomogram was built, which can be used by physicians to counsel patients. Ultimately, these findings can serve as a starting point to unravel factors associated with walking performance and develop a prognostic model.

In **chapter 6** we assessed the prevalence of incontinence in Dutch adult patients and described their referral and experiences with pelvic floor physiotherapy. This type of physiotherapy might be beneficial to patients with Pompe disease as pelvic floor muscles, which are part of the limb-girdle region, might be involved in incontinence. During their regular follow up all Dutch patients were asked about symptoms of incontinence and were followed if referred to pelvic floor physiotherapy. One in two patients reported incontinence. Based on both patients' opinions and patient files from physiotherapists, it seems that pelvic floor physiotherapy, aimed at normalizing the tonus of the pelvic floor musculature, may be beneficial to these patients. More standardized prospective studies are needed to assess this further.

Chapter 7 discusses the main findings of our studies, our experience with the current physiotherapeutic care as well as standardized exercise training and contains suggestions for future research.

SAMENVATTING

De ziekte van Pompe is een zeldzame erfelijke metabole myopathie en lysosomale stapelingsziekte. Het wordt veroorzaakt door een tekort aan het lysosomale enzym zure alfa-glucosidase, dat nodig is om glycogeen in de lysosomen af te breken. Als gevolg van deze tekortkoming stapelt glycogeen in verschillende weefsels, vooral in spieren. Dit leidt tot het verlies van spierkracht en spierfunctiefunctie en leidt uiteindelijk tot rolstoel- en beademingsafhankelijkheid.

In 2006, is enzymvervangingstherapie (ERT) beschikbaar gekomen voor alle patiënten met de ziekte van Pompe, waardoor de perspectieven van patiënten zijn veranderd in termen van verbeterde overleving, toegenomen spierkracht en loopafstand en stabilisatie van de longfunctie. Niet alle patiënten reageren echter even goed, en niet alle spierschade en functionele beperkingen kunnen worden opgelost. Daarom blijft het belangrijk om aanvullende manieren te vinden om de fysieke functie van deze patiënten zo goed mogelijk te houden. Fysiotherapie heeft tot doel de voordelen van enzymvervanging te maximaliseren en het maximale niveau van functie, functionele onafhankelijkheid en participatie te bevorderen en te handhaven. Er zijn echter geen richtlijnen voor fysiotherapeutische zorg voor de ziekte van Pompe.

Dit proefschrift heeft als doel te onderzoeken of fysiotherapeutische zorg voor patiënten met de ziekte van Pompe een waardevolle aanvulling kan zijn op de bestaande ERT en hoe deze zorg kan worden georganiseerd. De studies opgenomen in dit proefschrift onderzoeken de verwijzingspatronen naar hedendaagse fysiotherapeutische zorg en hun inhoud (zowel reguliere

fysiotherapie als bekkenfysiotherapie), het gebruik van training om het functioneren van patiënten te verbeteren (afgezien van eventuele verbeteringen verkregen uit ERT), evenals risico's factoren die van invloed zijn op het loopvermogen van patiënten.

Hoofdstuk 1 geeft een algemene inleiding met betrekking tot de ziekte van Pompe en fysiotherapeutische zorg. Het biedt achtergrondinformatie over de pathogenese, klinische presentatie en fysiotherapeutische zorg bij neuromusculaire aandoeningen.

Een overzicht van de hedendaagse fysiotherapiepraktijk in Nederland wordt gegeven in hoofdstuk 2. Een vragenlijstonderzoek werd uitgevoerd onder 88 volwassen patiënten met de ziekte van Pompe en 31 fysiotherapeuten. Minder dan 60% van de patiënten had ooit fysiotherapeutische zorg ontvangen voor symptomen die verband houden met de ziekte van Pompe. Op het moment van afname van de enquête werd minder dan 40% behandeld door een fysiotherapeut. Onze studie toonde aan dat behandelingsdoelen en interventies vaak niet in overeenstemming waren met de reden van verwijzing en dat de toegepaste behandelingsinterventies uiteenlopend en divers waren. Desondanks, gaf de meerderheid van de patiënten en fysiotherapeuten aan fysiotherapie als gunstig te ervaren. Er werd geconcludeerd dat er een grote behoefte is aan richtlijnen voor fysiotherapeutische zorg om verwijsredenen, behandeldoelen en behandelingen meer op elkaar af te stemmen.

In **hoofdstuk 3** en **4** hebben we de veiligheid, haalbaarheid en toegevoegde waarde van training naast de behandeling met ERT bestudeerd. Gedurende 12 weken volgden 25 patiënten drie keer per week een gecombineerd oefenprogramma, bestaande uit duur-, kracht- en rompstabiliteit oefeningen. In **hoofdstuk 3** hebben we de effecten geëvalueerd van dit oefenprogramma op

uithoudingsvermogen, spierkracht en -functie en rompstabiliteit. De effecten op pijn, vermoeidheid, en op fysiek en mentaal functioneren worden in **hoofdstuk 4** gepresenteerd. De training is door 23 patiënten succesvol afgerond. Met deze studie hebben we aangetoond dat het trainingsprogramma haalbaar en veilig is. Bovendien helpt de training het uithoudingsvermogen, de spierkracht, spierfunctie en rompstabiliteit te verbeteren. Daarnaast verbeterde het trainingsprogramma de tekenen van vermoeidheid en pijn en mentale gezondheid. Deze resultaten toonden aan dat deze training veilig kan worden uitgevoerd bij mild aangedane patiënten met de ziekte van Pompe en lijkt van toegevoegde waarde voor deze patiënten.

Het verlies van het vermogen om normaal te lopen is een van de meest prominente tekenen voor de ziekte van Pompe en er is aangetoond dat dit een grote invloed heeft op de kwaliteit van leven van patiënten. Daarom is bij de behandeling van deze patiënten het behoud van het resterende niveau van looprestaties van groot belang. In **hoofdstuk 5** hebben we factoren onderzocht die bij volwassen patiënten met de ziekte van Pompe van invloed kunnen zijn op de looprestatie, met focus op de rol van spierkracht van vier spiergroepen van de onderste extremiteit. Op basis van 107 patiënten vonden we dat looprestaties kunnen worden verklaard door leeftijd, geslacht, BMI, het gebruik van beademingsapparatuur en de spierkracht van heup abductoren en knie extensoren. Op basis hiervan werd een nomogram gebouwd, dat door clinici kan worden gebruikt om patiënten te begeleiden. Uiteindelijk kunnen deze bevindingen dienen als een startpunt voor het ontwikkelen van een prognostisch model.

In **hoofdstuk 6** hebben we de prevalentie van incontinentie bij Nederlandse volwassen patiënten met de ziekte van Pompe onderzocht en hun verwijzing en ervaringen met bekkenbodemfysiotherapie beschreven. Bekkenbodem

fysiotherapie kan gunstig zijn voor patiënten met de ziekte van Pompe, omdat bekkenbodemspieren, die deel uitmaken van het gebied van de romp, mogelijk betrokken zijn bij incontinentie. Tijdens hun reguliere follow-up werden alle Nederlandse patiënten ondervraagd over symptomen van incontinentie, waarvan één op de twee incontinentie meldde. Alle patiënten die incontinentie rapporteerden werden verwezen naar bekkenbodemfysiotherapie en verder gevolgd. Op basis van de opgevraagde patiëntendossiers van de behandelende bekkenfysiotherapeuten en de mening van de patiënten, lijkt bekkenbodemfysiotherapie, gericht op het normaliseren van de tonus van de bekkenbodemmusculatuur, gunstig voor deze patiënten. Meer gestandaardiseerde prospectieve studies zijn nodig om dit verder te beoordelen.

Hoofdstuk 7 bespreekt de belangrijkste bevindingen van onze studies, onze ervaring met de huidige fysiotherapeutische zorg en gestandaardiseerde training en bevat suggesties voor toekomstig onderzoek.

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ABOUT THE AUTHOR

Marein Favejee was born on 22 July 1974, in Harderwijk, the Netherlands. In 1993, she graduated from the Christelijk College Nassau Veluwe in Harderwijk. Hereafter she studied physiotherapy at the Hanze Hogeschool in Groningen. After obtaining her bachelor degree in 1998 she started working as a physiotherapist at the Tuberculosis Centre Beatrixoord in Haren. In the same time she started Human Movement Sciences at the University of Groningen. She obtained her master degree in 2001. Between 2001 and 2002 she worked as a physiotherapist at several institutes in Rotterdam.

From 2002 until the end of 2008 Marein has worked both at the department of Physiotherapy and the department of Orthopaedics at the Erasmus MC University Medical Center in Rotterdam.

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Marein lives in Rotterdam with Michel and their sons Philip, Julius and Olivier.

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PHD PORTFOLIO

Training	Year	ECTs
Biomedical English writing and Communication	2010	3.0
NIHES: Biostatistical methods I	2014	5.7
Basis cursus Regelgeving & Organisatie voor Klinisch Onderzoekers (BROK)	2015	1.0
Oral and poster presentations		
Afscheidscongres afdeling fysiotherapie, Rotterdam, The Netherlands- Oral presentation	2018	1.0
Spierziektecongres Vereniging Spierziekten Nederland (VSN), Veldhoven, The Netherlands - Oral presentation	2015	1.0
2nd UK Pompe Physio Discussion Day, Manchester, United Kingdom- Oral presentation	2013	1.0
Spierziektecongres Vereniging Spierziekten Nederland (VSN), Veldhoven, The Netherlands - Poster presentation	2012	1.0
Physical therapy Workshop, London, United Kingdom- Oral presentation	2012	1.0
Spierziektecongres Vereniging Spierziekten Nederland (VSN), Veldhoven, The Netherlands - Poster presentation	2010	1.0
3rd European symposium Steps Forward in Pompe disease, Munich, Germany	2009	1.0
MPS patient day, Amersfoort, The Netherlands- Oral presentation	2009	1.0
Physical therapy Workshop, Boston , United States of America– 2 Oral presentations	2009	2.0

Attended congresses and workshops		
Spark Investigators meeting, Milan, Italy	2019	0.5
AMICUS Investigators meeting, Munich, Germany	2019	0.5
AMICUS ATB200-03 Clinical Evaluator/ Physiotherapist training	2019	0.5
AMICUS ATB200-02 Clinical Evaluator/ Physiotherapist training	2017	0.2
Pompe disease expert day, Rotterdam , The Netherlands	2016	0.2
Sanofi Neo GAA-1 Clinical Evaluator/ Physiotherapist training	2013	0.2
Teaching		
Supervising bachelor-thesis	2018	1.0
Teaching of 4th year medical students at the Erasmus MC University	2009-2019	3.0
QMFT training BMN 701-301	2014	2.0
Other activities		
Journal club	2010-2017	1.0
Research meeting	2009-2019	1.0

ABBREVIATIONS

6MWT	6-minute walk test
ADL	Activities of daily life
AET	Aerobic exercise therapy
BMD	Bone-mineral density
BMI	Body mass index
CI	Confidence interval
CK	Creatinine kinase
ERT	Enzyme replacement therapy
FSS	Fatigue Severity Scale
FVC	Forced vital capacity
GAA	Acid α-glucosidase
HA	Hip abduction
HEP	Home exercise program
HF	Hip flexion
HHD	Hand held dynamometry
ICF	International Classification of Functioning, Disability and Health
IMT	Inspiratory muscle training
KE	Knee extension
KF	Knee flexion
MCS	Mental component summary
MEP	Maximal expiratory pressure
MIP	Maximal inspiratory pressure
MMT	Manual muscle testing
MRC	Medical research council
MSE	Muscle strengthening exercises
NMD	Neuromuscular disorders
OR	Odds ratio
PFM	Pelvic floor muscle(s)
PFPT	Pelvic floor physiotherapist
PCS	Physical component summary
QMFT	Quick Motor Function Test
QoL	Quality of life
RMT	Respiratory muscle training
RHS	Rotterdam Handicap Scale
R-PAct	Rasch-built Pompe-specific Activity Scale
SF-36	Short-form 36 health survey
VO_2 PEAK	Peak oxygen uptake
VT	Ventilator threshold
WMAX	Maximum workload capacity