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Aerobic And Resistance Exercise In Late-Onset Pompe Disease Treated With Enzymatic Replacement Therapy: A Systematic Review

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Abstract
Purpose: *to systematically review the current evidence on the effects of aerobic and resistance exercise in late-onset Pompe disease patients treated with enzymatic replacement therapy.*
Methods: *a systematic search of the literature was conducted on Academic Search Complete, Medline with full text, SPORTDiscus, Pubmed, and Science Direct electronic databases. In addition, cross-referencing and manual search of printed journals was performed. The eligibility criteria were (a) experimental or quasi-experimental research design; (b) intervention with aerobic exercise, resistance exercise, or both; (c) published studies until August 2016; (d) studies published in English, Spanish, French or Portuguese; (e) studies on human beings. This systematic review was reported in accordance with the PRISMA statement.*
Results: *of the 166 citations identified, 4 met the eligibility criteria and were included in the review. All studies had a small sample size, and ranged from 5 to 23 participants. In three of the studies, the training programs allowed subjects to improve physical parameters like muscular strength, endurance, core stability, and to decrease pain and fatigue. Overall, body composition remained unchanged.*
Conclusions: *the results found in this review suggest that aerobic and resistance training may be beneficial in this population. There is a need for additional, larger sample sizes, longer studies with more homogeneous training programs on this topic.*
Keywords: *aerobic exercise, glycogen storage disease type II, Pompe disease, resistance training, systematic review.*

I. Introduction

Among metabolic myopathies, Pompe disease belongs to glycogen storage diseases, also known as glycogenoses (thus, it is also called glycogenosis type II). First described in 1932, it is estimated that this rare, autosomal recessive disease affects 1 in 40,000 live births worldwide [1]. It is caused by lysosomal acid alpha-glucosidase gene defects (GAA, OMIM number 606800), for which more than 300 mutations have been described [2], having as a direct consequence the accumulation and deposition of glycogen in multiple organs, as GAA catalyzes the breakdown of glycogen into glucose in lysosomal acid environment [3].

In its infantile-onset form, the most severe clinical manifestations of Pompe disease are respiratory distress and heart failure, both in association with hypertrophic cardiomyopathy secondary to glycogen's deposition. On the other hand, in late-onset forms patients are mainly affected by progressive muscular weakness, with less cardiac and respiratory compromise [4]. The severity and clinical evolution of the disease vary depending on the specific mutation [5], with a range from less than 1% enzyme activity in most serious cases and up to 30% in moderate ones [1].

Nowadays, Pompe disease is the only glycogenosis for which a specific treatment exists [6]. In 2006, the United States, Europe and some other countries approved a biweekly 20 mg/kg enzymatic replacement therapy (ERT), administered intravenously with dose adjustment depending on tolerance or the presence of adverse events [7]. Since then, several clinical trials and observational studies have been developed to describe ERT effects on Pompe disease clinical evolution among children, adolescents and adults [7, 8]. This systematic review aims to evaluate the evidence on the benefits of aerobic and resistance exercise in late-onset Pompe disease patients treated with ERT, to identify scopes, limitations in current knowledge and possible actions in future research on this topic.

II. Methodology

2.1 Search strategy

Studies were retrieved between January and August 2016 based on the terms "exercise" and "Pompe disease" as well as related terms or synonyms (i.e., "training," "glycogen storage disease type II") on the following electronic databases: (1) Academic Search Complete, (2) Medline with full text, (3) SPORTDiscus,

(4) Pubmed and (5) Science Direct. An example (Pubmed) of the search strategy is (("exercise"[MeSH Terms] OR "exercise"[All Fields]) AND ("glycogen storage disease type ii"[MeSH Terms] OR ("glycogen"[All Fields] AND "storage"[All Fields] AND "disease"[All Fields] AND "type"[All Fields] AND "ii"[All Fields]) OR "glycogen storage disease type ii"[All Fields] OR ("pompe"[All Fields] AND "disease"[All Fields]) OR "pompe disease"[All Fields])) AND "humans"[MeSH Terms]. Specific research filters were applied in each database in order to better adjust the search according to eligibility criteria.

Studies that were not available as free full texts were tracked by librarians from the University of Costa Rica in order to purchase them or to contact authors for free access. In addition to electronic database research, a manual cross-referencing search was conducted alongside retrieved reviews and printed journals to identify potentially eligible studies. There were no restrictions on publication dates. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [9] was used to conduct and report this systematic review. All files were managed and stored in Mendeley Desktop® version 1.15.3. All data extracted from each study was coded and organized using Microsoft Excel® 2010.

2.2 Selection criteria

To be included, studies met the following eligibility criteria: (1) experimental or quasi-experimental research design; (2) exercise intervention with aerobic, resistance training, or both; (3) studies published until February 2016 **August 2016**; (4) studies published in English, Spanish, French or Portuguese; (5) studies in humans.

2.3 Study selection and data abstraction

Study selection and data abstraction were performed by the two authors, independently from each other. The following information was extracted: authors' information, publication year, publication country, age and sex of participants, disease duration since diagnosis and time since ERT began, sample sizes, characteristics of the exercise interventions (duration, frequency, intensity, length of each session, mode of training and supervision of exercise), outcomes measured and measuring instruments. Then, a meeting was scheduled to compare findings and discrepancies regarding eligibility, and data abstraction was resolved by consensus.

III. Results

Fig. 1 shows the PRISMA flow diagram of the search process, including the reasons for exclusion. Manual search and printed journals results are not shown on the "Identification" box because the results found were duplicates and, therefore, removed. Of the 166 citations identified, four met the eligibility criteria and were included in this review. Additional file 1 shows a list of each excluded study (n = 115), including the reason for the exclusions in each case. TABLE 1 describes exercise interventions and summarizes other important characteristics of included studies.

Each study had a small number of participants, which ranged from 5 to 23. There were 17 women (51.52%) and 16 men (48.48%) including all the four studies. Half of interventions were conducted in Greece and the other half in Holland. Findings reported by Favejee et al. [10] were based on the intervention described by van den Berg et al. [11]. Both authors evaluated multiple outcomes from the same sample, which explains why table 1 shows the same participant and intervention descriptions for both studies.

The 12 week aerobic, resistance training with core stability intervention conducted by van den Berg et al. [11] proved to be safe according to plasma creatine kinase, pain and fatigue periodic tests, and also allowed the participants to significantly increase their endurance (workload capacity before intervention 110 W, and 122 W after, 95% confidence interval of 6.0 to 19.7), maximum oxygen uptake ($p < 0.01$) and ventilatory threshold ($p < 0.01$); in addition, muscle strength of the hip flexors and shoulder abductors increases significantly ($p < 0.01$ and $p = 0.02$, respectively). In respect to muscle function, the participants spent less time climbing four steps ($p = 0.02$) and rising from supine to standing positions ($p = 0.05$). Furthermore, they increased their times in balance for each of the core exercises. On the contrary, Quick Motor Function Test

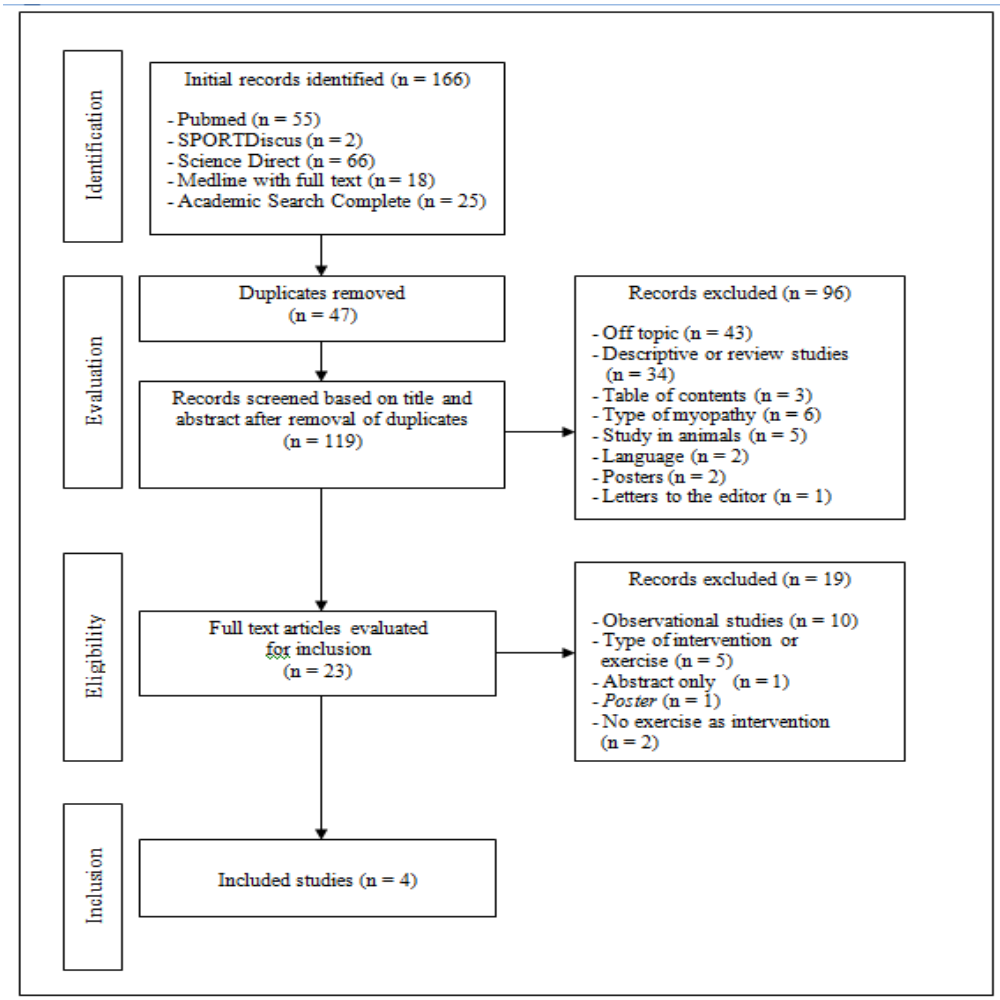

Fig 1. Flow diagram for research strategy and study selection, in accordance with PRISMA statement

TABLE 1. Main characteristics of the studies included

Study	Country	Sample characteristics	Characteristics of the exercise interventions	Exercise supervision	Main outcomes and measuring instruments
Favejee et al., 2015	Holland	N = 23 11 women, 12 men Age: 46 years(median) Disease duration: 16 years (median) Time since beginning of ERT: 3.1 years (median), range 1-6 years	Type of exercise: aerobic, RT and core stability Duration: 12 weeks Frequency: 3 times/week Length of each session: 60 – 90 min Training program in each session (in the following order): (1) 5 min warm-up HR 100-110 BPM. (2) 15 min cycle ergometer HR equivalent to 60% VO_2max. (3) RT: seated row, chest press, biceps curl (seated), leg press, leg curl, hip abduction and hip adduction. 3 sets of 15-20 repetitions at 70% of 4 RM. (4) 15 min cycle ergometer HR equivalent to 60% de VO_2max. (5) Core stability: abdominal bridge, back bridge, left side bridge, right side bridge. 3 sets of 30 seconds each one. (6) 5 min cooling-down HR 100-110 BPM.	Yes	Fatigue: FSS; Pain: questionnaire from the study. Activity level: speed test of 6MWT, QMFT, R-PAct, ActiGraph GT3X accelerometer. Health status: SF-36 version 2.
Terzis et al., 2011	Greece	N = 5 4 women, 1 man Age: women 48.75 years(mean), range 39-71 years; male subject 39 years Disease duration: not specified Time since beginning of ERT: at least 18 months	Type of exercise: aerobic and RT Duration: 20 weeks Frequency: 3 times/week Length of each session: not specified Training program in each session (in the following order): (1) 30 min stationary bicycle at 65-75% of MHR. (2) 10 min stretching, major muscle groups. (3) RT: ¼ squat, leg curls, knee raise, push-ups against a wall, back extensions, sit ups, ¼ overhead press, elbow extensions and elbow curls. First 3 weeks: 1-2 sets of 10 repetitions; Weeks 4-20: 3 sets of 10 repetitions. Each time at 50% of 10 RM, with 2 min rest between sets. (4) Stretching major muscle groups.	Yes	Strength: load transductor Tesys 800 (Globus Sport and Health Technologies, Italy). Muscle function: 6MWT. Body composition: DXA (DPX-L, LUNAR Radiation, U.S.)

Terzis et al., 2012	Greece	N = 5 2 women, 3 men Age: women 46.5 years (mean); men 39.67 years (mean) Disease duration: not specified Time since beginning of ERT: range 15 - 30 months	Type of exercise: aerobic and RT Duration: 6 months Frequency: 3 times/week Length of each session: not specified Training program in each session: - Between hospital sessions: same experimental design as in Terzis et al. (2011). Participants were performing that training protocol 10 months previous to initiation of exercise intervention for 6 months as described below. - During ERT infusion at the hospital (once every 2 weeks): (1) 30 min stationary bicycle at 65-75% of MHR. (2) 10 min stretching, lower limbs only due to ERT administration. (3) RT: half squat, leg curls (standing), hip adduction and hip abduction. 3 sets of 10 repetitions at 80% of 10 RM, with 2 min rest between sets.	Yes	Strength: load transductor Tesys 800 (Globus Sport and Health Technologies, Italy); Muscle function: 6MWT; Body composition: DXA (DPX-L, LUNAR Radiation, U.S.)
van den Berg et al., 2015	Holland	N = 23 11 women, 12 men Age: 46 years (median) Disease duration: 16 years (median) Time since beginning of ERT: 3.1 years (median), range 1-6 years	Type of exercise: aerobic, RT and core stability Duration: 12 weeks Frequency: 3 times/week Length of each session: 60 – 90 min Training program in each session (in the following order): (1) 5 min warm-up HR 100-110 BPM. (2) 15 min cycle ergometer HR equivalent to 60% VO_2max. (3) RT: seated row, chest press, biceps curls (seated), leg press, leg curls, hip abduction and hip adduction. 3 sets of 15-20 repetitions at 70% of 4 RM. (4) 15 min cycle ergometer HR equivalent to 60% de VO_2max. (5) Core stability: abdominal bridge, back bridge, left side bridge, right side bridge. 3 sets of 30 seconds each. (6) 5 min cooling-down HR 100-110 BPM.	Yes	Exercise safety: plasmatic creatine kinase every 2 weeks; Endurance: cycle ergometer Jaeger ER 800 (Jaeger, Germany), spiro-ergometry Oxycon Pro (Jaeger, Germany); Strength: hand-held dynamometry; Core stability: time (in seconds); Muscle function: 10 meter running, climbing 4 steps, rising from supine to standing positions, QMFT; Body composition: DXA (Lunar DPX, GE Health Care)

RT (resistance training); HR (heart rate); MHR (maximum heart rate); RM (repetition maximum); BPM (beats per minute); ERT (enzyme replacement therapy); QMFT (Quick Motor Function Test); FSS (Fatigue Severity Scale); R-PAct (Rasch-built Pompe-specific Activity Scale); SF-36 (Medical Outcomes Study 36-Item Short-Form Health Survey); DXA (dual X-ray absorptiometry); 6MWT (6-minute walking test).

(QMFT) scores, time to run 10 meters, and body composition (evaluated through dual X-ray absorptiometry) remained unchanged.

On the other hand, Favejee et al. found that the exercise intervention conducted by van den Berg et al. also decreased significantly both fatigue ($p = 0.01$) and pain ($p = 0.04$) among participants [10, 11]. Nevertheless, those changes were not correlated to the improvement in the physical parameters described by van den Berg et al. [11]. In addition, muscle function self-report scores, the amount of physical activity (measured through accelerometry) and general health status scores remained unchanged.

Terzis et al. [12] discovered that 20 weeks of supervised aerobic and resistance training enhanced muscular strength ($p < 0.05$) for hip extensions, bench pressing and rowing, as well as the distance covered in the 6-minute Walking Test ($p < 0.01$). Regarding body composition, lean body mass in upper limbs increased ($p < 0.05$); however, no changes in the body fat or in the bone mineral density were observed. Likewise, in a subsequent study conducted by Terzis et al. [13] in which the effects of physical exercise during the ERT infusion was evaluated after 6 months of training, no improvements in body composition, muscular strength or the distance covered in the 6-minute Walking Test were found.

IV. Discussion

The aim of this systematic review was to evaluate the current evidence on the benefits of aerobic exercise, resistance training or their combination in late-onset Pompe disease patients treated with ERT. The findings suggest that interventions with physical exercise in this population may enhance muscular strength and endurance, along with a decrease in pain and fatigue. Furthermore, according to van den Berg et al. [11] those improvements seem to be independent of the beneficial effects of ERT alone, a finding that suggests that exercise may be recommended as a complementary, non-pharmacological, effective treatment in the clinical management of these patients. Nevertheless, these results must be interpreted with caution, due to small sample sizes and the short length of the studies conducted on this topic so far.

In recent years, some investigations have examined the effectiveness of aerobic and resistance training among patients with other muscle diseases. For instance, Voet et al., based on findings from randomized and quasi-randomized controlled trials, concluded that there was insufficient evidence to support the prescription of resistance training in patients diagnosed with myotonic dystrophy and facioscapulohumeral dystrophy [14]; on the contrary, in patients with mitochondrial myopathies the combination of aerobic exercise and resistance training appeared to be safe, and allowed participants to improve submaximal aerobic endurance. Similar results for several myopathies were found by Féasson et al. in their review [15].

Correspondingly, other muscle glycogenoses have been studied to determine the benefits of physical exercise, as in McArdle disease (glycogenosis type V). So far, the findings indicate that aerobic exercise improves exercise tolerance and endurance [16–18]. In addition, the review by Lucia et al. includes nutritional recommendations as well as exercise prescription examples for these patients [19]. Despite all of the above, until now no high methodological quality randomized or quasi-randomized controlled trials have been conducted with McArdle patients to evaluate the effects of exercise [20], just like in Pompe disease for which, to the best of the author's knowledge, no randomized controlled trials have been conducted or published so far.

Several observational studies have reported favorable changes in muscular strength, muscle function, endurance, fatigue and quality of life among patients with late-onset Pompe disease [21–27]. However, such studies focused on describing and reporting the effects of ERT on those outcomes (for example, motor function or endurance before and after ERT administration), which prevent to conclude on the effects of exercise *per se*, independently from ERT known benefits.

The findings of this systematic review, as well as the observed heterogeneity in the design of exercise interventions, lead us to recommend that future studies on this field include larger samples. In spite of the low incidence of glycogenosis type II, and considering that the blinding of participants in exercise interventions is probably impossible, we suggest that randomized or quasi-randomized trials are conducted to increase methodological quality and conclude with greater certainty about the effectiveness of aerobic and resistance training in this specific population.

V. Conclusion

In summary, despite only four studies met inclusion criteria, our findings suggest that physicians and sport coaches may prescribe physical exercise as an adjunct, inexpensive, safe and effective treatment to improve aerobic endurance, muscular strength and function in patients with late-onset Pompe disease treated with enzymatic replacement therapy. There is a need for additional, larger sample sizes, longer studies with more homogeneous training programs on this topic to give more accurate recommendations when prescribing exercise in this population.

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