Review Article

Nutrition and exercise in Pompe disease

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Abstract: The current standard of care for Pompe disease (PD) is the administration of enzyme replacement therapy (ERT). Exercise and nutrition are often considered as complementary strategies rather than "treatments" *per se*. Nutritional assessment is important in patients with locomotor disability because the relative hypodynamia limits energy expenditure and thus the total amount of energy must be reduced to avoid obesity. A lower total energy intake often leads to lower protein and micronutrient intake. Consequently, ensuring that Pompe patients are tested for and replaced for deficiencies (protein, vitamin D, vitamin B12, etc.) is an important aspect of care. Furthermore, given the role of autophagy in the pathophysiology of PD and the fact that fasting induces autophagy, it is important that strategies such as nutritional timing and amino acid intake (L-arginine, L-leucine) be evaluated as therapies. Exercise interventions have been shown to improve six-minute walk testing distance by more than what was seen in the seminal ERT study in late-onset PD. Exercise therapy can also activate autophagy, and this is likely another component of its efficacy. The current review will evaluate the theoretical and practical aspects of nutrition and exercise as therapies for patients with PD.

Keywords: Protein intake; diet; exercise training; strength; endurance; autophagy

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Introduction

Pompe disease (PD) is due to acid alpha-glucosidase (GAA) deficiency, which causes accumulation of lysosomal glycogen and autophagic buildup, leading to progressive skeletal muscle (SM) deterioration, functional impairment, and disability (1). Lifestyle and dietary factors, such as physical inactivity and inadequate food intake, may also accelerate disease progression in patients with muscle disease. For example, a low energy, protein and/or micronutrient intake may limit the ability to withstand infections and other metabolic stressors (2). Another common complication of muscle weakness is avoidance of physical activity (PA), which lowers energy expenditure and predisposes for weight-gain. Consequently, in order to maintain bodyweight, patients with muscle disease often consume too few calories, including key nutrients for maintaining SM mass, such as protein (3). The invariant oro-pharyngeal dysphagia that accompanies infantile-onset Pompe disease (IOPD) (4), and occasionally the late-onset form (LOPD) (5,6), further complicates the ability to maintain safe and adequate oral intake. From a weight-management perspective, it is therefore often not possible to reduce energy intake further, which predisposes to obesity, as previously described in some Pompe patients (7). A reduction in muscle mass and increase in body fat are interactively deleterious to health, as seen in older adults with sarcopenic obesity (8). The role of low SM mass (cachexia) combined with excessive body fat is likely underappreciated in patients with muscle disease. Therefore, ensuring an adequate energy intake that provides sufficient protein to maintain SM mass and function, whilst

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preventing body fat gain, is a delicate balancing act in PD patients, and more research is warranted in this area.

One strategy to enhance SM mass, strength and function is resistance exercise training (RET) and this has been used successfully in a wide variety of muscle diseases (9-13). Endurance exercise training (AET) is classically associated with improvements in aerobic capacity, and several studies have found improvements in fitness and/or functional capacity in patients with primary muscle disorders (14-17) and metabolic myopathies (18-20). More recently, high intensity interval training (HIIT), by itself or when combined with regular AET and RET, has been shown to improve fitness in fascio-scapulo-humeral muscular dystrophy (MD) patients (21,22). Combined endurance and resistance exercise programs have also been shown to improve muscle strength in Pompe patients (10,23-25). A common issue with both IOPD and LOPD is progressive restrictive ventilatory failure (1,26). Several forms of respiratory muscle exercise training have been successfully described in MD (27-29). More recently, several studies have shown that respiratory exercise training is helpful in PD (30-32).

The purpose of this review is to describe the major clinical challenges associated with providing nutritional and exercise guidelines to children and adults with PD. The nutritional section will cover our current knowledge on body composition and habitual nutrient intake in PD patients, and delineate specific supplementation strategies to mitigate obesity and SM deterioration in this population. The exercise section will provide a general overview of the benefits of mixed exercise training (AET and RET), how it mitigates PD progression, and why it should be used as an adjunct to enzyme replacement therapy (ERT) in LOPD. We will then discuss the rationale for combining both exercise and dietary intervention to mitigate PD progression.

Body composition

The physical manifestation of low energy and protein intake is cachexia, and this is reflected in low muscle mass, often estimated in large population studies using body mass index (BMI) [wt (kg)/ht (m)^2]. A BMI of <18.5 is considered underweight and is suggestive of cachexia whilst values ≥30 suggest obesity. Given that it is the actual amount of muscle and fat that are most important in determining nutritional adequacy and individual recommendations, a more accurate determination of these metrics is required in research and clinical care. Dual energy absorptiometry (DEXA) has become a gold standard tool for the determination of body composition (body fat and lean mass) and bone density in neuromuscular disease and aging research (33).

DEXA scanning was used to evaluate body composition in nine LOPD patients and found that whilst the BMI indicated obesity in only one patient (38.7), eight of the nine were obese based upon body fat (>30% body fat) and three patients were over 50% body fat (7). Further indicating the inadequacy of BMI in the evaluation of individual patients was their finding that the patient with the lowest BMI (19.1, close to underweight) had a body fat percentage of 38.7% (e.g., obesity) (7). Another study found that the average percent body fat in five LOPD patients was in the obese range at ~45% (23). Consequently, it appears that obesity is a significant issue in LOPD patients and is concerning for it will increase the risk of obesity-associated morbidities (34), especially when combined with low PA (35-37). Furthermore, the extra weight is a major issue in a patient with SM weakness and will further impair activities of daily living (ADL). Unfortunately, the results of a 20-week exercise intervention study showed that the percent body fat did not change in spite of significant functional improvements (23). The latter findings are similar to results in able-bodied middle-aged men and women (38,39), suggesting that exercise must be combined with significant dietary restrictions in order to lower the percent body fat once a patient is already obese.

DEXA scanning has also found a low bone mineral density (BMD) in a high proportion of Pompe patients (40-42), and that low BMD correlated with muscle weakness (41). The latter effect is likely related to the known stimulatory effect of muscle contraction on osteoblasts (synthesis) and the failure of osteoblast activation with reduced mechanical stimuli (43,44). As expected, the low bone mass in Pompe patients further declines over time (40). Muscle weakness and low BMD are a dangerous combination for they lead to an increased fall risk and subsequent fracture risk (45,46). A femur or hip fracture in a patient who is very weak can be the seminal event resulting in a permanent loss of ambulation and can even lead to higher mortality risk (47). To what extent the low BMD seen in some Pompe patients is due to hypodynamia, low vitamin D status, and/or low protein intake is unclear, but all are likely contributors to some extent in specific patients and all are modifiable.

The above data suggests that many Pompe patients have low lean body mass (muscle) and high body fat, suggesting sarcopenic obesity. Furthermore, BMI is an inadequate tool for the individual assessment of Pompe patients. The data

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also suggests that DEXA scanning of all patients will help to assess lean muscle mass, body fat and bone density and allow for the ability to follow and quantify changes over time in response to various interventions. Furthermore, it will also allow for a more accurate assessment of body composition to identify issues at an early stage where intervention may be preventative (i.e., lower energy intake if obese, calcium/vitamin D if osteopenic, and bisphosphonates if osteoporotic). Finally, the DEXA scan analysis can be used as another marker for the efficacy of an intervention such as ERT or exercise.

Protein turnover and dietary concerns for Pompe patients

At the cellular level, the net protein balance of a tissue or whole body is a function of protein synthesis—protein breakdown/oxidation. Exercise and nutrition are important independent and interactive determinants of protein balance (48-50). For example, it has been well documented that acute bouts of resistance exercise lead to a more positive net muscle protein synthesis in healthy younger and older adults (48,51,52). It has also been shown that the provision of high-quality proteins [e.g., milk-based (whey and casein) and eggs (53)] synergistically enhance the protein stimulatory effects of resistance exercise. Importantly, these stimulatory effects are more potent for milk- *vs.* plant-based proteins (e.g., soy) (54,55). The superiority of milk and egg proteins over plant-based proteins is due to the higher biological value of the former, which contain a more balanced complement of the essential amino acids. Of the essential amino acids, leucine (a branched chain) appears to be the most potent in stimulating protein synthesis through mTOR activation (56).

There has only been one study that has looked at protein turnover is LOPD patients (N=5) and they reported a higher leucine rate of appearance (crude measure of protein breakdown) and a mild increase in leucine oxidation with a higher alanine rate of appearance all when expressed per lean body mass (57). Metabolic studies have also shown that altered nutrient sensing contributes to a greater protein breakdown in PD (58). Collectively, the above data suggests a net loss of protein through protein breakdown/oxidation that eventually leads to the canonical observation of lower muscle mass in patients. Interestingly, Raben's group recently demonstrated that GAA KO mice exhibit an impairment in the mTOR signalling pathway with sequestration of mTORC1 to the lysosome due to a lysosomal acidification defect and constitutive excess of TSC2, which ultimately inhibits mTORC1 activity (despite being localized to the lysosomal membrane) and impairs protein synthesis (59-61). They also demonstrated that the addition of L-arginine to $GAA^{-/-}$ animals leads to an increase in mTORC1 activation by TSC2 inhibition, which may remove autophagic buildup by inhibiting transcription factor EB (TFEB) and autophagosome formation (59). From a therapeutic perspective, L-leucine supplementation also shows promise for activating mTORC1 and augmenting protein synthesis in PD patients. For example, it was recently demonstrated that the addition of cell-permeable leucine to cell culture from an IOPD patient and L-leucine to the $GAA^{-/-}$ murine PD model, led to substantial mTORC1 activation and improvements in running, muscle mass and spontaneous activity (62). As such, it is plausible that leucine-induced mTORC1 activation will alleviate the buildup of new autophagosomes by inhibiting TFEB, albeit by a different mechanism than arginine (in this case TSC2 independent) (62). However, more research is needed to discern which amino acid is the most safe and effective adjunctive therapy to ERT in PD. To date, the only amino acid that has been evaluated in LOPD patients is the non-essential amino acid alanine that was added to a high protein diet plus exercise by Slonim *et al.* (63,64); however, given the open design and co-intervention it was not possible to determine whether alanine was independently and/or interactively beneficial.

Most of the nutritional recommendations for Pompe patients have emphasized the importance of a high protein diet (63,65-67). There is some evidence that a high protein diet can alter the impairments in protein turnover seen in PD (57). From the functional perspective, one case report (68), and a case series (64), reported improvements in body composition and/or muscle function in Pompe patients after a high protein diet intervention. In contrast, a small study (N=5) found improvements in protein turnover but no clinically relevant benefits from a high protein diet (57). Two small scale studies have found improvements in respiratory function in Pompe patients with a high protein diet (66,69). A longer-term (2–10 y) study in 34 patients with PD found that those who complied with a high protein diet (25–30% energy from PRO +1.5 g alanine 4 times a day) had a slower rate of physical decline over time (63); however, the latter study had no control group, and the intervention was both a nutritional and exercise intervention; consequently, it was unclear what proportion of the effect was attributed to each of the interventions or

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other factors.

To date, there have been no systematic evaluations of plasma vitamin and mineral levels in patients with PD; however, our data in MD patients (3), would predict that a substantial number of Pompe patients will also have a hypoenergetic dietary intake and a low intake of many micronutrients (vitamins and minerals). For example, our group found that 12/12 of our LOPD patients had plasma vitamin D levels that were insufficient (<75 nmol/L) and 4/12 were below the deficiency (<30 nmol/L) range (Tarnopolsky *et al.*, 2019, unpublished observations). Further supporting the importance of measuring and treating low vitamin D levels comes from the observation that a substantial proportion of patients have low BMD (41,70). From a practical perspective, it would be reasonable to consider suggesting a balanced multi-vitamin that meets the minimal daily requirement for the given country and provide 2,000 IU/d vitamin D supplementation to all LOPD and 1,000 IU/d to all IOPD patients outside of equatorial regions, unless contraindications would preclude this.

There have been very few studies looking at specific supplements in LOPD patients in contrast to the many evaluating creatine monohydrate in MD (71-74). A Cochrane review of the literature found that creatine monohydrate supplementation was associated with an 8.5% increase in muscle strength in MD (75); however, myotonic MD type 1 patients appeared to show no effect (73,74). Given the similarities between MD and PD, it is likely that at least some of the benefits reported in MD would be seen in PD; however, this remains a study that requires further evaluation. Another intervention that has been informally discussed but not formally studied in the PD population is the ketogenic diet (http://www.pompewarriorfoundation.com/research/). A ketogenic diet is usually >60% fat with very low carbohydrate (<50 g/d). The possible theories suggested for improving PD are that ketones (B-OH-butyrate and acetoacetate) can enhance muscle mass in MD (76), lower inflammation (77), activate chaperone-mediated autophagy (78), and that a very low carbohydrate intake is a form of substrate reduction therapy (SRT). The potential benefit of SRT was shown in the murine Pompe model with genetic knock-down of glycogen synthase leading to improved function (79). Practical issues with the ketogenic diet are issues of long-term compliance and care to ensure adequate micronutrient intake. Another concern is the potential to increase neutral lipids in the liver and lead to non-alcoholic fatty liver disease (NAFLD) and hepatic insulin resistance (80,81). Clearly, with the anecdotal evidence of "benefit" it is important that this concept be first evaluated in the murine model and if successful, in a randomized human clinical trial.

Exercise, health-span, and longevity

While the effects of habitual PA on 'health-span', mortality risks, and longevity are unknown for many rare diseases, findings in the general population largely extend to other human conditions. Cumulative evidence amassed over the last 50 years unequivocally show that sedentary living predisposes to chronic disease, disability, and premature death (82,83). Conversely, regular exercise, such as RET and AET, provides multi-systemic benefits that protect against morbidity, all-cause mortality, and extend average life expectancy (84-87). The reduction in all-cause mortality is primarily attributed to enhanced maximal aerobic capacity (VO_2max), but also to protection against obesity, type 2 diabetes, cancer, osteoporosis, hip fracture, depression, anxiety, and cognitive decline (88-93). Although vigorous exercise is particularly effective in reducing mortality risks (84,94), low-to-moderate intensity PA also confers substantial pro-longevity benefits and is more suitable for patients (95).

Exercise adaptations

The canonical adaptations to endurance and strength training are listed in *Table 1*, and these generally apply to special populations as well, including LOPD patients. As discussed, VO_2max is a strong predictor of all-cause mortality and may be improved by AET, which augments cardiac output (e.g., stroke volume) and systemic oxygen extraction (e.g., vasodilatory function, capillary density, and mitochondrial volume) (96,97). Other well-known adaptations to AET include a reduction in fat mass, improved insulin sensitivity/glucose regulation, and an enhanced blood lipid profile. Similarly, strength training reduces mortality risk, but by augmenting indices closely related to SM and bone mass, including muscle function (strength, endurance, and power), ADL, fall risk and institutionalization (98,99). For these reasons, AET is considered the cornerstone of cardiometabolic disease prevention, while RET is mainly used as a tool to combat age- and disease-related muscle loss (e.g., sarcopenia and cachexia, respectively). For increased efficacy, RET may be combined with oral supplementation of high-quality protein (e.g., whey and casein) (100). From a clinical perspective,

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Table 1 Primary adaptations and benefits of aerobic (AET; top) *vs.* resistance (RET; bottom) exercise training

Aerobic exercise training (AET)
Primary adaptations-cardiovascular:
Increased maximal aerobic capacity
Reduced resting HR
Reduced blood pressure (diastolic and systolic)
Expected myocellular benefits:
Oxidative phenotype shift (type IIx to type IIa)
Increased capillary density
Mitochondrial biogenesis
Fortified antioxidant defense (e.g., damage mitigation)
Augmented recycling (e.g., garbage/damage removal)
Improved quality control and repair
Expected whole-body benefits:
Improved body composition (e.g., body fat reduction)
Elevated basal metabolic rate
Improved insulin response, glucose regulation, and blood lipid profile
Anti-inflammatory effects/immune system boost
Resistance exercise training (RET)
Primary adaptations-musculoskeletal:
Increased anaerobic capacity
Muscle growth (e.g., fiber CSA-type I, type IIa, and type IIx)
Enhanced strength and power
Expected whole-body benefits:
Enhanced physical functioning (ADL, posture, and flexibility)
Improved body composition (mainly muscle/bone mass)
Elevated basal metabolic rate
Improved insulin response and glucose regulation
Anti-inflammatory effects
Expected cardiovascular benefits:
Some improvements in maximal aerobic capacity
Reduced blood pressure (diastolic)

ADL, activities of daily living.

it is important to recognize that there is significant overlap between the two exercise modes. For example, weight-bearing AET (e.g., walking, running, and cycling) provides a small but significant anabolic stimulus to muscles and bones (101), and RET may also improve cardiovascular function, albeit to a lesser extent than endurance training (102,103).

Exercise hormesis—the molecular basis

Concomitant accumulation of danger-associated molecular patterns (DAMPs), including oxidative damage, protein aggregates, and lipofuscin, is a common feature of biological aging, neurodegenerative disease, and lysosomal storage disorders (104-107). Intervention strategies that rejuvenate the organelles/systems that regulate ATP and ROS production (mitochondria), waste recycling (autophagosome, lysosome, and 26 proteasome), and protein quality control (unfolded protein response, UPR^{ER} and UPR^{MT}) may mitigate garbage buildup (e.g., 'autophagic blockage') and thereby preserve critical organ function (108). Exercise is an acute stress signal (ROS, Ca^{2+}, pH, and hypoxia) that activates evolutionary conserved cell danger response programs (CDR and DDR, respectively), lowers the energy state of the cell (NAD^+/NADH and AMP/ATP ratios), and promotes the release of neurotransmitters, hormones, and circulatory factors (e.g., exerkines), which coordinately stimulate mitochondrial biogenesis (CaMK II, PGC-1α, SIRT1, and AMPK), antioxidant defense (Nrf2-Keap1, NFκB, and MAPK), waste processing (ULK1-Beclin1, TFEB, and FOXO3a), and the immune response (NLRP3, IL-1β, IL-6, IL-10, IL-1ra, sTNF-R, and IL-18) (107-118). Repeated exposure to acute, non-lethal stress, such as AET, results in cellular adaptation into a more stress-resistant level, signified by rejuvenated mitochondria, fortified antioxidant defense, reduced oxidative damage/garbage buildup, and improved immunity (e.g., concept of exercise hormesis) (107,108,119,120). Collectively, there is a strong molecular basis for using exercise therapy in PD management, but a combined approach consisting of mixed AET/RET and intermittent supplementation of specific micronutrients, high-quality proteins, and amino acids (see text for details), may be necessary to maintain critical organ reserves, functional capacity, and independence in LOPD patients (*Figure 1*).

Exercise guidelines

Numerous position stands, authoritative reviews, and meta-analyses conclude that AET and RET should be prescribed together in concurrent/mixed training

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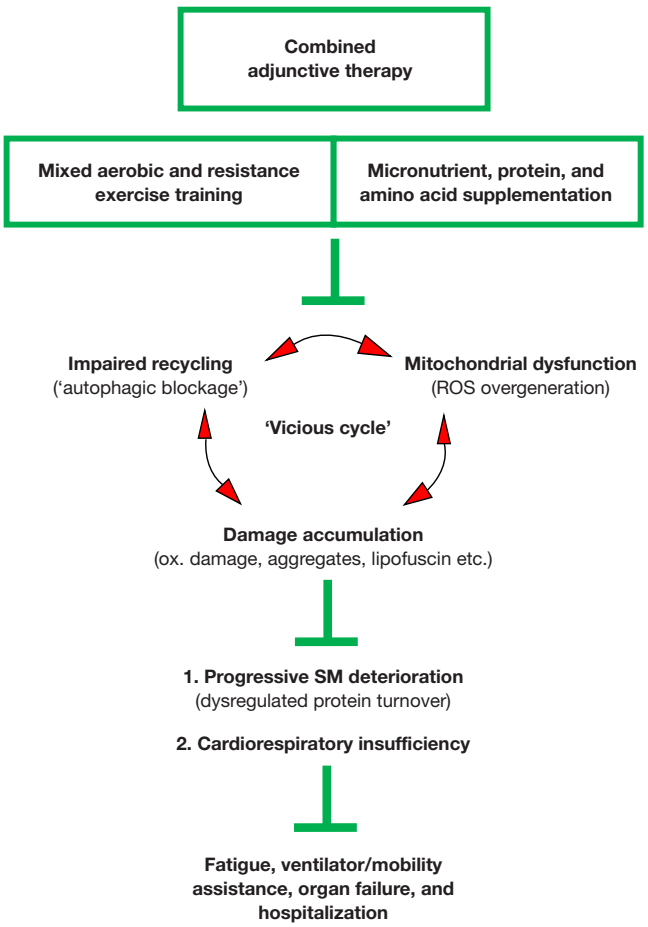

Figure 1 Theoretical basis for using mixed AET/RET and supplementation in Pompe disease management. Image is adapted from Nilsson *et al.* with permission (108). AET, endurance exercise training; RET, resistance exercise training.

programs to maximize health benefits (91-93). For example, a traditional, mixed training protocol consisting of 16–20 weeks of AET (3–5 d/week at 50–75% VO_2max) and RET (2–3 d/wk at 65–85% 1-RM) is sufficient to bestow the vast majority of the proven benefits of AET and RET in untrained individuals (*Table 1*). Considering the low risk-benefit ratio, LOPD patients are encouraged to engage in low-to-moderate intensity exercise under supervision on most days of the week (95,121-123). Clinicians and physical therapists should adhere to the standard exercise principles for untrained individuals [e.g., FITT formula-frequency, intensity, time, and type (124)], keeping in mind that excessively strenuous exercise, particularly with an eccentric component, may exacerbate muscle deterioration (123). Gentle strengthening exercises and stretching with a focus on functionality are therefore recommended, while overwork weakness, excessive fatigue, and muscle pain should be avoided (121,123). Notably, the safety and efficacy of mixed RET, AET, and core stability training were recently demonstrated in LOPD patients (discussed in the next section) (10,23,25), but in view of the substantial therapeutic benefits of AET alone, it may be the preferred single modality, with exercise intensities as high as 60–70% VO_2max (e.g., ~70–80% HRmax) well-tolerated (122).

Exercise therapy in LOPD patients

In general, exercise trials are lacking in LOPD and in the majority of those that have been completed, the number of patients have been too low to draw definite conclusions about safety and efficacy. Perhaps the first suggestion of the potential benefit of exercise in PD came from the "nutrition and exercise therapy (NET)" reported by Dr. Slonim's group (64). This case series reported on 34 Pompe patients who followed a nutrition (low carbohydrate + high protein + alanine 1.5 g four times a day) and exercise (45–50 min of aerobic treadmill walking at ~65% $VO2_{peak}$ + 10–15 min of arm ergometry) program for two–ten years (63). They found that the Walton scores (a measure of function) plateaued or improved in the 26 compliant patients whilst, declining in the eight non-compliant patients (63). It is difficult to know what proportion of the benefits could be attributed to the exercise and what could be attributed to the nutritional intervention in the latter study given that there was a co-intervention.

Another study indirectly evaluated exercise interventions using 6 minute walk distance in 44 Pompe patients before and after 12 months of ERT where they completed a sub-group analysis in five patients who did cycle ergometry every 2 weeks during the ERT infusion, with three subjects also doing "regular physiotherapy" (125). Each of the five patients showed improvements in the 6-MWT and ranked # 3,4,5,6,12 of the 21 patients (6 of the non-exercisers showed no improvement or a loss in performance) who completed the 6-MWT before and after the 12 month ERT trial (125). Again, there were confounders for only 3 of 5 participants did regular physiotherapy exercise (endurance-based), and with the small sample size it was impossible to determine of the benefit was from enhanced ERT uptake and/or the regular exercise.

In addition to the obvious benefits of increased aerobic capacity/fitness to an adult with PD (35,126), endurance exercise is likely to be of benefit to Pompe patients for other

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specific reasons including; a reduction in the risk of type 2 diabetes (127), and a reduction in body fat [obesity is more common in Pompe patients (7)]. Fatigue is also a common feature in adults with PD with severe fatigue reported in ~66% of cases (128). Even if only a portion of the fatigue in a Pompe patient has a central generator, a potential benefit from AET is likely to be lower peripheral and central fatigue. Finally, it is possible that AET and/or performing endurance exercise during ERT may enhance ERT uptake by the working muscle [greater capillarization, increased blood flow, increased number of mannose-6-phosphate receptors (125)]. Unfortunately, the potential for a synergistic effect of exercising whilst receiving ERT did not appear to improve function in a small study with five late onset Pompe patients (24); however, the initial evaluation of 6-MWT and strength in this study occurred after several months of both ERT and exercise and this would make it difficult to determine the effect of exercise during ERT for the largest effects (ERT + exercise) had already occurred (24).

A protean manifestation of PD is muscle weakness (1). Several studies have found that a RET program increased muscle strength in patients with MD (9,12). It is conceptually attractive to hypothesize that resistance exercise would also increase strength and ultimately function in patients with PD, yet only a few studies have been completed to date (10,23,25). Terzis and colleagues used a progressive resistance exercise program (following an aerobic cycling warm-up) for 20 weeks in 5 Pompe patients who had received ERT for one year (23). They reported improvements in muscle strength in four exercise tasks ranging from + 18.7–50.8% (3 of 4 statistically significant), and a significant increase in arm FFM (23). Importantly, they also found an increase in 6-minute walk test distance (6-MWT) with a very strong statistical relationship between hip extension strength and the 6-MWT (23). Although there was an endurance exercise component to the training, it is likely that most of the strength outcomes were a direct result of the resistance training component of the program (23). In a separate study, van der Ploeg's group examined the effects of mixed AET (60% VO_2max, 2×15 min), RET (70% 4-RM, 3 sets ×15 reps, 6 exercises), and core stability (4×30 sec, 4 exercises) training on aerobic capacity, body composition, muscle strength, and function (10,25). Significant improvements in VO_2max, 6-MWT, hip flexor strength, shoulder abductor strength, core stability, 4-step stair-climbing, and time-to-stand from supine position were reported, while body composition and pulmonary function (FVC) did not change. The latter finding stresses the importance of a dedicated program to improve FVC in LOPD. Another important finding of this study was that moderate-intensity mixed exercise is safe and well-tolerated since 23 out of 25 patients completed the training program. In the future, it will be important to determine the independent and interactive benefits of RET and AET in a larger cohort of patients and in children.

Exercise therapy in Pompe mice

To further evaluate the biochemical and molecular mechanisms behind a potential benefit of exercise in Pompe patients, we evaluated several outcome metrics in the $GAA^{-/-}$ murine model of PD (105,129). Wild-type controls and $GAA^{-/-}$ mice were randomly allocated to a progressive 14-week AET program (45 min, 5 d/wk) or a sedentary lifestyle with 50% also receiving bi-weekly ERT (40 mg/kg) nested within the exercise and sedentary allocations (129). To address the issue whether acute increases in blood flow enhance ERT uptake, we also added another cohort of $GAA^{-/-}$ mice that exercised for 30 min (warm-up), followed by an infusion of ERT (40 mg/kg) and a 60 min post-injection run at 15 m/min. The uptake of ERT did not appear to be enhanced in either muscle or heart with acute endurance exercise (as reflected by GAA enzyme activity). In addition, fourteen weeks of ERT was associated with an approximate doubling of GAA activity in both heart and quadriceps muscle in the $GAA^{-/-}$ mice with no further enhancement from AET. Although ERT alone enhanced grip strength in treated animals, it did not improve aerobic fitness (maximal running test) or motor function, dynamic balance, and dexterity (rotarod test) to the same extent as the mice receiving polytherapy (e.g., ERT and AET). Finally, glycogen clearance was nearly 100% in heart and soleus (slow-twitch muscle) *vs.* ~40–80% complete in fast-twitch muscles (quadriceps, plantaris, and diaphragm) in both ERT-treated groups (with and without EX), but was not independently affected by exercise alone or synergistically enhanced in mice receiving polytherapy (ERT + EX) (129).

The above data strongly suggest that the clinical benefits of AET reported in LOPD patients (24), are due to mechanism(s) independent of enhanced removal of glycogen. Our follow-up analyses indicated that AET rejuvenated the mitochondrial-lysosomal axis, and that the fast-twitch muscles of the polytherapy-treated mice (ERT + EX) exhibited less oxidative damage and autophagic buildup compared to unexercised controls (105).

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Considering that contractile activity stimulates antioxidant (Nrf2-Keap1, NFκB, and MAPK) and recycling (TFEB, FOXO3, and ULK1-Beclin1) pathways, AET may have mitigated 'autophagic blockage' in the polytherapy group. Although the clearance of autophagic debris by AET has yet to be shown in humans, and it is difficult to extrapolate our findings, it is interesting that the initial clinical sign reported by most LOPD patients is impaired exercise capacity (1). Since a lack of endurance and balance/coordination issues lead to functional impairment and increased fall-risk, respectively, the functional metrics reported in our mouse study may have clinical relevance.

Respiratory training in LOPD patients

Given that respiratory weakness is a major cause of morbidity and mortality in both IOPD and LOPD patients (1,6,26), strategies that could improve respiratory muscle strength/function could have very significant long-term benefits. In fact, respiratory function was the co-primary outcome in the seminal study evaluating the effect of rGAA ERT in LOPD (130). The first study to evaluate respiratory muscle strength training used a device that provided 60% of the maximal inspiratory and expiratory strength with 25 repetitions twice a day six days a week (31). The duration in the two patients varied from 12 to 32 weeks, yet the increases were ~73% for inspiratory strength and 31–48% for expiratory strength (31). This same group used a 12-wk respiratory muscle strength protocol in eight LOPD patients followed by 12 weeks of detraining (30). They reported a 19.6% increase in maximal inspiratory pressure and a 16.1% increase in maximal expiratory pressure in the eight patients (30). Importantly, these gains were maintained during the 12 weeks of detraining (30). A similar increase in maximal inspiratory pressure (strength) of 15.7% at 6 weeks and 26.4% at 52 weeks was reported with progressive inspiratory muscle strength training in 11 LOPD patients (131). There is only one report of respiratory muscle training in IOPD with five patients on full time ventilation requirements and four on part-time requirements (32). They trained for 90 days using 3–4 sets of 6–10 inspiratory efforts with a modified threshold inspiratory training device, and then received adenovirus GAA gene therapy directly to the diaphragm and continued training for ~ one year (32). The exercise training alone (90 day before gene therapy) leads to a significant increase in peak inspiratory flow and a trend for an increase in tidal volume (32). Collectively, the above data show that inspiratory and combined inspiratory/expiratory muscle strength training improves important metrics of respiratory function ~15–45% in LOPD patients, and there appears to be some improvement even in ventilator dependent IOPD patients. Importantly, none of the studies showed any evidence of serious side effects attributable to the therapy such as a pneumothorax.

Conclusions

Many patients with PD show evidence of sarcopenic obesity with a low muscle mass and high body fat percentage. Furthermore, a high proportion show low BMD that can be a precursor to osteoporosis and fracture risk. The best way to determine the body composition in an individual patient is a DEXA scan. The cause of the aforementioned body composition alterations is likely sub-optimal protein intake combined with excessive energy intake that is compounded by muscle weakness and lower amounts of PA. Patients should consume protein intake levels (~1.2–1.4 g/kg/d) above those recommended for the general population (0.8–1.0 g/kg/d) but it is unclear if very high levels (>1.6 g/kg/d) would confer benefit or may lead to excessive energy intake. To optimize the muscle protein synthesis effects of protein it is suggested that proteins of higher biological value be consumed (milk, whey, eggs, lean meat and fish). It is likely that the low energy intakes required by relatively inactive patients would also lead to sub-optimal vitamin intake, as we have shown in MD patients (3), with vitamin D being most likely to be deficient in non-equatorial regions. A balanced multi-vitamin supplement would likely be a reasonable suggestion for most patients given the likely low total energy intake.

At this point, it is not clear whether specific amino acid supplementation would confer functional benefits to Pompe patient. It is theoretically attractive to consider an interactive exercise-nutrition program, for example, consumption of high quality proteins enriched with leucine in conjunction with RET for augmenting mTOR activity and protein synthesis or L-arginine supplementation combined with AET (or intermittent fasting) for TFEB activation and increased autophagic flux , although such strategies remain to be elucidated. The data in MD patients would suggest that creatine monohydrate would improve muscle strength in Pompe patients (75); however, this should be evaluated specifically in Pompe patients in the future. Similarly, although there are theoretical reasons to speculate that a ketogenic diet could confer benefits in PD,

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this has not yet been studied in murine models or patients.

Exercise confers many health benefits to able-bodied men and women and these will very likely extend to those with neuromuscular disorders including PD. Animal studies suggest that the benefits come from an enhanced autophagy and mitochondrial biogenesis and not an increase in the delivery or uptake of ERT. Similarly, the hypothesis that exercise during ERT will improve uptake has not been supported by animal studies, nor proven in human trials. The combination of both endurance and RET programs for Pompe patients has been shown to improve strength and function substantially and this combined approach also fits with the theoretical optimal program for patients and older adults. Given the involvement of the respiratory system in LOPD and IOPD, it is encouraging that specific respiratory exercise training improves respiratory capacity. The effects of exercise reported to date are actually above the current ERT benefits (130). For example, 18 months of ERT was associated with a 28.1 m improvement in the 6-MWT (130), whilst 5 months of ERT combined with endurance and resistance exercise led to a 44.4 m improvement in the 6-MWT (23). Furthermore 18 months of ERT was associated with a 3.4% improvement in respiratory capacity (130), with several months of respiratory exercise being associated with a ~18–50% increase in respiratory capacity (30,31). Overall, exercise training appears to be a safe, effective and inexpensive intervention to improve functional metrics of importance to the health of Pompe patients.

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Footnote

Conflicts of Interest: Drs. Tarnopolsky and Nilsson have shares in Exerkine Corporation and the company has filed a patent on the use of a ketogenic compound for the treatment of Pompe disease. Dr. Tarnopolsky has received speaker honoraria from Sanofi-Genzyme.

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