Review Article

Pompe disease: what are we missing?

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Abstract: Pompe disease is a multisystemic metabolic disorder caused by a deficiency of lysosomal acid alpha-glucosidase (GAA) leading to progressive accumulation of lysosomal glycogen, lysosomal swelling and rupture in all tissues of the human body. Furthermore, autophagic buildup, organelle abnormalities, and energy deficit are regularly observed. Enzyme replacement therapy has been available for patients living with Pompe disease for more than 15 years. Although our disease knowledge has grown enormously, we still have multiple challenges to overcome. Here, I will discuss unmet clinical needs, neglected or overlooked aspects of the pathophysiology, and issues related to future therapies.

Keywords: Pompe disease; energy metabolism; fatigue; axial myopathy; enzyme replacement therapy (ERT); gene therapy; unmet needs

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Background

Pompe disease (glycogen storage disease type II; OMIM #232300) is caused by mutations in the *GAA* gene leading to the absence or reduced levels of lysosomal acid alpha-glucosidase (GAA) activity in all tissues of the human body (1,2). Lysosomal glycogen accumulation results in the swelling and rupture of lysosomes and subsequently cell damage, organelle dysfunction, and alterations in energy demand of the cell (3).

Pompe disease is divided in the infantile form [infantile-onset Pompe disease (IOPD)] with a multisystem storage of accumulated lysosomal-, and non-lysosomal-bound glycogen e.g. in the heart, skeletal muscle, and brain tissue. The later onset form [late-onset Pompe disease (LOPD)] manifests with predominant but not exclusive skeletal muscle involvement (4). Since the licensing of alglucosidase alfa (a recombinant human GAA) 15 years ago, this drug is the therapy of choice for all patients living with Pompe disease (4-8). The implementation of enzyme replacement therapy (ERT) has been a huge leap forward but the disease is still far from being cured. Where do we fall short?

Unmet needs and open questions

Fatigue—an energy deficit?

Limitation of human endurance during constant-power exercise has been referred to as the point of exhaustion or fatigue. The connection between power output or speed and time to fatigue is well defined: maximal neuromuscular power can only be maintained for a few seconds, and humans have a high capacity to sustain exercise if the power or speed requirements are fairly low. Also, the sustainable power output declines in a characteristic pattern. The sustainable power is usually no more than 20–30% of the maximal power, which is equivalent to about 70% of the power output associated with maximal oxygen uptake (9). Interestingly, peripheral fatigue in healthy humans contributes to muscle growth by increasing motor unit recruitment and decreasing muscle fiber shortening velocity during strength training. These changes increase the mechanical tension experienced by the muscle fibers controlled by high-threshold motor. Initial symptoms in adults living with Pompe disease are linked to neuromuscular non-structural dysfunction, e.g., resulting in

a decline of stamina and strength while climbing staircases, rising from a chair, walking longer distances, or practicing sports. Thus, first symptoms in LOPD are related to a neuromuscular fatigue by cellular energy supply deficits, ending up in some patients in muscle cramping (10-15). Common denominator for physiological fatigue in adults with Pompe disease is peripheral in nature. In this context, one has to clearly separate "energetic", non-structural myasthenic-like reduced stamina from structural, atrophy-related muscular weakness within the fatigue spectrum. Furthermore, diaphragmatic ventilatory compromises may exacerbate both, non-structural and structural fatigue, thus contributing to differences and interpretation of the widely used combined outcome measure, the 6-minute walking test in clinical trials (16). The situation is even more complex in infantile and juvenile Pompe disease considering the central nervous system involvement (17,18): a central structural component may contribute to the physiological fatigue in this age group along the afferent and efferent pathways of the primary somatic sensory and motor cortex, brainstem motor nuclei, anterior horn cells in the spinal cord, and neuromuscular synapses (19). Glycolysis is the enzymatic change of glucose to pyruvate, which produces two net ATP molecules per molecule of glucose. Cells in oxygen-rich environments are capable to use oxidative phosphorylation (OXPHOS) for more effective ATP production, which nets an average of 34 additional ATP molecules per glucose by oxidizing pyruvate to acetyl coenzyme A (acetyl-CoA), then to carbon dioxide and water in the mitochondrial tricarboxylic acid (TCA) cycle. Consequently, mitochondria play a fundamental role in cell energy metabolism with the need of a strict quality control. So, what is the GAA enzyme function in relation to energy supply in the skeletal muscle cell, and how it affects the cross-talk with the mitochondrial energy distribution and the fatty acid beta-oxidation? We hardly have answers to these questions right now. Morphologically, beyond glycogen storage and autophagic buildup, abnormal mitochondria are commonly found in muscle tissue of Pompe disease patients at all ages. Changes include larger than normal mitochondria, granular or paracrystalline inclusions, and mitophagia, a selective autophagy that occurs to specifically remove damaged mitochondria, mostly located in the inner part of a skeletal muscle fiber (20-24). Our own pilot study in human myoblasts from Pompe patients revealed a reduced basal respiration and reduced glycolysis, pointing to a cellular energy crisis (Meinke *et al.* in this journal issue). A reasonable explanation is a defective mitophagy, an inept elimination of damaged mitochondria through the autophagic pathway. Abnormal and functionally altered and aged mitochondria are likely to remain in skeletal muscle despite any type of therapy, particularly considering the inability of ERT to fully reverse lysosomal glycogen accumulation and autophagic defect in this tissue. Hence, these abnormalities in the cellular energy metabolism may represent an additional obstacle for the long-term treatment efficacy. As for the physiological fatigue in Pompe disease, is it possible that insufficient GAA activity facilitates the formation of a "metabolic block" similar to that observed in glycogenosis type V (McArdle's disease) caused by myophosphorylase deficiency? Myophosphorylase cleaves the outer 1,4-α-glycosyl branches of the glycogen molecule, releasing glucose-1-phosphate that enters glycolysis. People living with McArdle's disease experience exercise intolerance due to the defect in muscle glycogenolysis, since glycogen is the primary fuel early in exercise and at moderate to high exercise intensities. The "second wind" phenomenon after 7–10 min of exercise characterized by bradycardia and perceived effort, so that exercise can be reperformed. This phenomenon is attributed to a surplus delivery of hepatic glucose and free fatty acids from adipose tissues to the contracting muscles, which is facilitated by an exaggerated sympathoadrenal response during exercise (25). However, performing a bout of treadmill exercise does not lead to a reduction of glycogen in McArdle mice, whereas in exercising wild-type mice, glycogen is metabolized to near depletion (26). Analysis of different muscles [soleus, extensor digitorum longus muscle (EDL), tibialis anterior muscle (TA), and quadriceps] from homozygous McArdle mice demonstrated that glycolytic muscles respond to glycogen accumulation by inhibiting glycogen synthase, which is likely due to fiber type-dependent metabolic adaptation. The quadriceps from the McArdle mouse exhibits pronounced changes in glucose metabolism, while the distal muscles such as TA, EDL, and soleus demonstrate little change in glucose metabolism (26). Interestingly, dramatic increases in protein levels of GLUT4, hexokinase II and F6PK (6-phosphfructo-2-kinase) of the glycolytic pathway were found in patients with McArdle disease and in a mouse model (26). McArdle patients do adapt to their energy deficit by increasing the ability to take up glucose for direct glycolysis and by increasing hepatic glucose output and fatty acid oxidation (26). What do we know about these metabolic adaptations in distinct muscles in Pompe disease? We have not yet looked methodically at the components of the glycolytic pathway in the diseased muscle cells, such as

for example GLUT4, hexokinase II or F6PK.

Even more puzzling is the role of muscle satellite cells (SC) in this context. What is the metabolic status of quiescent satellite cells (QSCs) and how does metabolism control the transition of QSC to activated and differentiated states? A very recent study on the regulation of skeletal muscle regeneration provides some clues (27). QSCs gain mitochondrial activity by the aerobic SC niche combined with a surplus usage of glycolytic pathway. This aerobic glycolysis (the Warburg metabolism) is supposed to allow SCs to respond to the rapid increase in energy demand that characterizes the activated state. It also provides glycolytic intermediates, which are critical building blocks for synthesis of amino acids, lipids, and nucleic acids that are required for SCs division and replication (27). Chen *et al.* (27) demonstrated that the ubiquitously expressed transcription factor Yin Yang 1 (YY1) regulates skeletal muscle regeneration through controlling metabolic reprogramming of SCs. Deletion of YY1 in Pax7 expressing cells led to a failure of diaphragm muscle development, and inducible deletion of YY1 in SCs severely impaired acute muscle regeneration. YY1 deletion resulted in cell-autonomous defect in SCs activation and proliferation, pointing to its role as a key regulator of SCs expansion. Simultaneously, YY1 also stabilizes Hif1a protein to activate Hif1a-mediated glycolytic genes. Loss of YY1 led to up-regulation of mitochondrial genes and inhibition of glycolysis, thus causing the defect in SCs activation (27). These findings are of great interest, as recent reports provide convincing evidence that skeletal muscle repair falters precisely at the step of SC activation in Pompe disease (28,29). The French and Dutch groups found that the satellite cells pool is preserved and fully functional in response to acute muscle injury in Pompe disease; however, there is no active muscle regeneration despite progressive glycogen accumulation and muscle damage (see review by Schaaf *et al.* in this issue). In sum, beyond defective autophagy, a mis-regulation of transcription factor YY1 may contribute to the observed failure of SC activation in Pompe disease. Modulators of SCs transcription factors may therefore open new avenues for therapy in Pompe disease and other neuromuscular disorders.

More questions related to the pathogenesis

What do we know about the cellular pH after lysosomal rupture? Is there enough buffering capacity in each cell to equalize the acidic shift after glycogen overloaded lysosomal rupture? Is it possible that the shift in cellular acidity triggers autophagy, mitophagy, and fibrosis, e.g., in infantile-onset cases? An opposite scenario appears even more reasonable. It is well established that in the early neonatal period when the placental supply of nutrients is interrupted and the demand for glucose is very high, autophagic delivery of glycogen takes place in liver and muscle (30,31). This acute and massive autophagic transfer of glycogen to the lysosome may cause them to rupture and spill glycogen and potential toxic substances to the cytoplasm. What can be done about it?

Also, what about the osmotic pressure of glycogen overload in the cells? Actually, we don't even have an answer to what seems to be a straightforward question—how glycogen gets to the lysosome and why? What is the contribution of the released glucose to the energy status of the cells? Finally, is the accumulated glycogen structurally normal?/or does it exist as acid insoluble proglycogen and acid soluble macroglycogen?

Translating this back to patients, what type of metabolic food intake (protein-rich or ketogenic diet) and training (aerobic versus anaerobic, concentric versus eccentric) are best for people with Pompe disease? How do we fine-tune the nutrition and exercise and adjust them to a particular stage of the disease progression? (see review by Tarnopolsky and Nilsson in this issue). To give a solid scientific answer to these questions, we have to address these cellular metabolic consequences in more detail under clinical trial conditions, especially with a more adequate long-term read-out of the physiological fatigue. We also need to develop adaptive new types of exercise training protocols in Pompe disease, as this may help increase lysosomal glycogen turnover rates, tone down autophagy, and prolong non-fatigued lifetime (14,32,33).

Paraspinal axial weakness and atrophy

This condition preexists, persists, and worsened during the disease course, and axial paraspinal muscles seem hardly reachable by ERT (34-36). Why is this so? In general, information on paraspinal muscle myopathology is scarce and was only recently summarized (37). Predominance of type I muscle, neurogenic changes, type II myofiber atrophy, and a higher number of ragged red and cytochrome oxidase-deficient myofibers have been reported in healthy paraspinal musculature (37-39). Non-diseased paraspinal muscles show age-dependent multiple structural abnormalities, e.g., core, moth-eaten myofibers, split myofibers, and neurogenic fiber type grouping (38). A link

between tendon tension and structural changes in paraspinal muscles was suggested (39). In the context of Pompe disease, of particular interest are the findings by Zimmermann and colleagues showing that in healthy subjects mitochondrial changes with reduced complex I, cytochrome c oxidase, and citrate synthase can be found, and up to 35% of the selected muscle fibers can be acid phosphatase positive (40). This brings us to the findings seen in camptocormia, also known as bent spine syndrome, a greatly incapacitating condition that occurs in various disorders, particularly in Parkinson's disease. Camptocormia in Parkinson's disease manifests with similar myopathic changes, namely type I myofiber hypertrophy, loss of type II myofibers, loss of oxidative enzyme activity, and again a high number of fibers with acid phosphatase reactivity. Ultrastructurally, myofibrillar disorganization and Z-band streaming are reported. The mitochondrial content of paraspinal muscles in patients and controls is markedly higher than in limb muscles, and the severity of the clinical syndrome is linked to the degree of the myopathic changes (41). The authors argued that a dysregulation of the proprioception could be a part of the pathogenesis of camptocormia in Parkinson's disease, particularly in view of the clinical symptoms of rigidity and loss of muscle strength (41). In case of Pompe disease, a combination of ridged tendon tension, specialized energetic compartmentation by accumulation of mitochondria, and lysosomal storage pathology may all contribute to the early paraspinal axial atrophy in Pompe disease. Why is this important for people living with Pompe disease? Is lower back pain, a frequently reported symptom in Pompe disease, related to paraspinal muscle atrophy? In model athletes like astronauts, both cross-sectional area and paraspinal muscles attenuation decline after long-duration spaceflight. Of note, the erector spinae and multifidus muscle need 12 months to recover, whereas psoas and quadratus lumborum muscle attenuation remain reduced even 2 to 4 years post spaceflight. Spaceflight-induced changes in paraspinal muscle morphology may contribute to back pain commonly reported in astronauts (42). Finally, we need to explore the correlation between the thoracic paraspinal muscle atrophy and respiratory function as a surrogate maker of ventilator insufficiency and early mortality in Pompe disease.

Outcome measures for clinical trials and long-term follow-up: a "deepBodyGestalt" approach

Presently we cast our lot with mostly old-fashioned clinically meaningful differences for clinical trials. Covering the wide spectrum of phenotypes in untreated and ERT treated people living with Pompe disease is a challenge for any new therapy. Here, new technologies and methods, presently used for diagnostic purposes, such as, for example, deepGestalt (43) and face@gene (44) may soon come in handy. A "deepBodyGestalt" monitoring approach embedded in a whole-body imaging framework combined with a personalized molecular signature will enhance our current phenotype stratification and thereby improve the short- and long-term monitoring of the efficacy of novel therapeutic approaches.

Unmet needs in pharmacological therapy: considering "gene transplant"

Why do we see the progression of a decline in response to ERT after three to 5 years? The uptake of alglucosidase alfa occurs via the cation-independent mannose 6-phosphate (CI-M6P) receptor followed by delivery of the enzyme to the lysosome by receptor-mediated endocytosis. There is an amazing amelioration of lysosomal glycogen burden in cardiac tissue but less so in other tissues including skeletal muscle. Only 1% of the intravenously administrated alglucosidase alfa is taken up into skeletal muscle. The question is whether repeated activation of CI-M6P receptor can lead to its saturation, desensitization, and finally resistance, as reported for the long-term treatment with β2-adrenergic agonists and glucocorticoids in asthma and other autoimmune diseases (45-47). Furthermore, β2-adrenergic receptor desensitization and downregulation may account for adverse reactions due to enhanced release of pro-inflammatory mediators (48). Consequently, it is not clear if the use of long-acting selective β2-receptor agonists in Pompe disease is a good choice in the long run (49). In addition, we know almost nothing about posttranslational modifications of the CI-M6P receptor and its turnover rate in human skeletal muscle. These issues may be relevant to liver directed gene therapies for Pompe disease. As for the moment, gene therapy clinical trials have already begun, and next-generation enhanced GAA enzymes are being tested in ongoing clinical trials.

Importantly, we still have to solve the issue of ERT dosing. The reality is that many infants and juveniles already receive 40 mg/kg per week. Shall we double or quadruple the dose in declining LOPD patients? There is no "obvious" answer to this question. To prove the point, we need an investigator driven clinical trial with a crossover head-

to-head design of escalating ERT dosages. Nevertheless, physicians do need some flexibility to prescribe high dosage. Yet another but related question is how much GAA activity is needed for normal cell metabolism in different tissues.

Although very promising, gene therapy for Pompe disease is still at the early stages, and the search for alternative viral vectors continues. An important issue here is the safety and efficacy of repeat administration of viral vectors, and several groups are already addressing this hurdle (50,51) (see several reviews on the subject in this issue). We have to accept that any type of vector-mediated gene therapy is a "gene transplant approach"; so, we have to implement immunosuppression strategies right from the start. Finally, we need to explore combination therapies, e.g., GAA gene therapy boosted by ERT, or ERT supported by autophagy-targeted treatment or glycogen substrate reduction therapy. And last, but not least, there is an urgent need to explore intrathecal administration and implant reservoirs, particularly for the treatment of the central nervous system in IOPD (52,53).

In conclusion, there is plenty of work to do. We need to keep on pulling in one direction to achieve the best-personalized treatment for each person living with Pompe disease.

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