Title: Genes and exercise intolerance: Insights from McArdle disease

Short running title: McArdle disease.

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ABSTRACT

McArdle disease (glycogen storage disease type V) is caused by inherited deficiency of a key enzyme in muscle metabolism, the skeletal-muscle specific isoform of glycogen phosphorylase, ‘myophosphorylase’, which is encoded by the PYGM gene. Here we review the main pathophysiological, genotypic and phenotypic features of McArdle disease and their interactions. To date, moderate-intensity exercise (together with pre-exercise carbohydrate ingestion) is the only treatment option that has proven useful for these patients. Further, regular physical activity attenuates the clinical severity of McArdle disease. This is quite remarkable for a monogenic disorder that consistently leads to the same metabolic defect at the muscle tissue level, that is, complete inability to use muscle glycogen stores. Further knowledge of this disorder would help patients and enhance understanding of exercise metabolism as well as exercise genomics. Indeed, McArdle disease is a paradigm of human exercise intolerance and PYGM genotyping should be included in the genetic analyses that might be applied in the coming personalized exercise medicine as well as in future research on genetics and exercise-related phenotypes.

Key words: myophosphorylase, genomics, rhabdomyolysis, exercise, glycogenosis type V.
**Definition**

Glycogenosis type V [glycogen storage disease type V (GSD V), McArdle disease or myophosphorylase deficiency; OMIM® database number 232600] is a disorder of skeletal-muscle carbohydrate metabolism originally described by the Scottish physician Brian McArdle in 1951.(30) This autosomal recessive disease is caused by pathogenic mutations in both copies of the phosphorylase, glycogen, muscle (abbreviated as \(\text{PYGM};\) MIM # 608455) gene encoding the muscle-specific isoform of glycogen phosphorylase, 'myophosphorylase'.(24) There is a paucity of data on prevalence of the disease, however recent studies suggest that it has been traditionally underestimated (8, 35) and might range from 1:50,000 to 1:200,000. Although this disorder belongs to the group of rare diseases (ORPHA368), it is the commonest muscle glycogenosis.

Myophosphorylase is the only isoform of glycogen phosphorylase expressed in skeletal-muscle tissue as opposed to the two other isoenzymes, which are encoded by \(\text{PYGL}\) (liver isoform) and \(\text{PYGB}\) (brain) gene, respectively. As such, McArdle disease is a ‘pure’, relatively benign myopathy as opposed to other metabolic disorders (such as Pompe disease -GSD II), where more tissues and organs besides skeletal muscles are severely affected, potentially leading to a fatal outcome. This, together with the fact that McArdle disease is a paradigm of exercise intolerance in humans (see below), makes it a unique model of study in the field of sports medicine, muscle physiology and exercise genetics.(48) The first case of a patient ever described, a 30-year old man, George W., was quite eloquent: ‘For as long as the patient could remember, light exercise of any muscle had always led to pain in the muscle...weakness ad stiffness...chewing sometimes gave rise to pain in the masticatory muscles’.(30)

Myophosphorylase catalyzes the breakdown of muscle glycogen into glucose-1-phosphate in muscle fibres. Thus, patients are unable to obtain energy from their muscle glycogen stores.(9) Nonetheless, glycolysis is blocked upstream, and thus the muscle fibres of McArdle disease patients can still take up glucose from the blood and convert it into glucose-6-phosphate, which then enters glycolysis (24) (Figure 1). For this reason, muscle glycolysis is not totally impaired in these patients.

**Main clinical features**

Irrespective of the specific defect (whether affecting lipid or carbohydrate metabolism or the respiratory chain), all genetic disorders that alter energy supply to the skeletal
muscle essentially result in one of two main syndromes, chronic (‘fixed’) muscle weakness or exercise intolerance. Although the latter is most commonly caused by McArdle disease, it might be also caused by other inherited defects in enzymes of muscle glycolysis (see also Figure 1): phosphofructokinase (GSD VII or Tarui disease), phosphorylase b kinase (GSD VIII), phosphoglycerate kinase (GSD IX), phosphoglyceromutase (GSD X), lactate dehydrogenase (GSD XI) or ß-enolase (GSD XIII).(9)

‘Exercise intolerance’ typically consists of acute crises of undue fatigue and muscle pain and stiffness (followed by contractures), especially at the start of exercise sessions that are much attenuated upon exercise cessation.(24) These crises can lead to severe muscle damage or rhabdomyolysis, as reflected by a massive release of muscle proteins, eg, creatine-kinase (CK) or myoglobin, into the blood. Thus, high serum CK activity (typically >1,000 U/L) and ‘dark urine’ (due to myoglobinuria) are frequent after exercise.(25) The main potential threat of exercise rhabdomyolysis is acute renal failure or eventually hyperkalemia, but these episodes are rare.(25) These possible risks, together with the unpleasant symptoms of exercise intolerance, explain why clinicians have traditionally advised these patients to refrain from exercise practice.

A frequent characteristic is the report by most patients of the ‘second wind’ phenomenon, that is, a marked improvement in exercise capacity after ~10 minutes of dynamic exercise, eg, brisk walking; exercise capacity is improved due to an attenuation of muscle pain and tachycardia, both of which occurred shortly after the start of exertion (see also Figure 2).(25) Additional features of the disease are that ~25% of patients develop ‘fixed weakness’ and wasting affecting mostly proximal trunk muscle groups. This phenomenon has been attributed to the cumulative effect of repeated episodes of rhabdomyolysis,(61) but this hypothesis remains to be proven. In general, McArdle’s condition is aggravated with aging (32, 55) but it is hard to separate this from the fact of insufficient physical activity (PA).

**Pathophysiology of exercise intolerance**

Patients’ exercise intolerance is usually triggered by muscle tasks that predominantly involve (aerobic/anaerobic) glycolysis for ATP production.(24) Thus, ‘muscle crises’ are typically triggered by vigorous dynamic exercise (eg, brisk walking, stair-climbing, sprinting to catch a bus) and especially by ‘static’ (or isometric) contractions relying on
smaller muscle groups as well as on anaerobic metabolism, eg, lifting/carrying weights or handgrip exercise. Not only glycolytic capacity, but also muscle oxidative phosphorylation (OXPHOS) capacity is usually impaired due to the block in glycogenolysis. Indeed, the ability of muscles to produce pyruvate, a molecule that plays an anaplerotic role in the Krebs cycle, is severely impaired in these patients. This results in a marked decrease in skeletal-muscle capacity for ATP synthesis through OXPHOS, and in accumulation of ADP and Pi in muscle fibres.

High intracellular concentrations of ADP and Pi can potentially inhibit the myofibrillar ATP-ase, the sarcoplasmic reticulum Ca\(^{2+}\) ATPase (SERCA1) pump and the Na\(^{+}\)-K\(^{+}\) ATP-ase (or ‘pump’) reactions; leading to decreased contractility and premature fatigue (Figure 2). Deficient glycogen-dependent ATP supply can result in further down-regulation of Na\(^{+}\)-K\(^{+}\) pumps in the skeletal muscle fibres of patients and in impaired membrane excitability and muscle cramping. In this regard, lactic acidosis does not necessarily impair muscle performance and could in fact protect against muscle fatigue (see (6) for a review), eg, owing to its beneficial effect on muscle membrane excitability. The fact that McArdle patients fatigue so easily despite their muscles producing very small lactate amounts (ie, their exercise peak lactate levels do not hardly surpass 2mM/l) means they represent an ideal, highly sought after physiological model which can be used in the study of normal muscle metabolism. Notably, this disease has partly allowed to unveil the fact that lactate is by no means a ‘metabolic poison’ to working muscles.

The causes for exercise rhabdomyolysis in these patients remain to be clearly established. Because they can induce structural muscle fiber fragility and cause membrane disruption, possible causative mechanisms are the mechanical stress imposed by high muscle glycogen stores, down-regulation of muscle Na\(^{+}\)-K\(^{+}\) pumps (which are responsible for maintaining cellular volume and integrity), or increased oxidative stress. Finally, besides causing muscle fatigue and cramps, elevated Ca\(^{2+}\) levels in the sarcoplasm (owing to the abovementioned down-regulation in SERCA1) might activate proteases, phospholipases and other catabolic enzymes that cause structural damage.
Muscle biopsy (typically in the *vastus lateralis* or the *biceps brachialis*) has been traditionally used to perform histochemical and biochemical analysis. Histochemistry of muscle specimens shows high subsarcolemmal/intermyofibrillar glycogen deposits and negative myophosphorylase reaction, with the latter being corroborated at the biochemistry level with the undetectable enzyme activity. However, current best practice for confirmatory diagnosis of McArdle disease is the use of genetic testing. Ideally, patients should be diagnosed by showing they are homozygous or compound heterozygous for pathogenic *PYGM* mutations. The frequency of certain *PYGM* gene mutations in any population can vary and so the more prevalent mutations (notably, the p.R50X mutation –see below), should firstly be tested. This approach can shorten the time for genetic diagnosis, since full *PYGM* gene screening includes analysis of 20 exons. Diagnosis from muscle biopsy is usually unnecessary, except when no mutations are found after sequencing the *PYGM* gene. Although these cases are very rare, they require muscle biochemical diagnosis and analysis of the mutations from muscle RNA.

The first *PYGM* pathogenic mutations were described in 1993 (5, 54) and a total of 151 mutations have been described up to date in the *PYGM* gene (~91% being exonic and and 9% intronic). The main types of mutations are missense (accounting for 50% of all described mutations), followed by deletions (19%), nonsense mutations (13%), and mutations that affect the splicing (11%). The p.R50X (or p.Arg50*) mutation, located in exon 1, is clearly the most prevalent among Caucasian population, usually accounting for ≥50% of the mutant alleles (see (33) for a review) whereas in patients of Asian descent it has only been described in a Korean patient. Most reported mutations have functional consequences, and many in fact result in no gene transcript levels owing to a homeostatic mechanism, the so-called non-sense mediated decay (NMD), which regulates the quality of the transcripts inside each cell by degrading those that contain premature termination codons. The action of NMD explains, at least partly, why except three cases reported in the literature (2 North-Americans (56) and one Japanese individual (49)) patients typically present *null* myophosphorylase activity in muscle biopsies, eg, 69% of all registered Spanish patients and actually 100% in whom muscle biopsies were analyzed.
Currently we do not have a worldwide view of the \textit{PYGM} mutations at all. In-depth studies are needed in those areas where this information is essentially lacking, which basically includes all the continents except some European countries and the US. Further, using next-generation sequencing De Castro and co-workers (8) recently suggested that the currently accepted disease prevalence in US Americans of European descendent (~1/100,000) is an underestimation. Thus, the actual prevalence would be at least two or even three times higher in this population compared to the data we recently reported for Caucasian Spaniards, ~1/167,000.\(^{(25)}\)

**Insights from the Spanish registry of patients: regular physical activity modulates disease phenotype**

In January 2010, the number of genetically diagnosed cases in Spain was 239 (102 female) and their \textit{PYGM} genotype as well as their phenotype characteristics were reported in detail.\(^{(25)}\) Virtually all had exercise intolerance (although the intensity/type of the exercise stimuli triggering such crises varied considerably among individuals -see below) as well as high serum CK levels; also, the majority reported the ‘second wind’ phenomenon. Yet only five years later, we have identified ~100 new patients based on Sanger \textit{PYGM} sequencing, which translates to a prevalence of ~1/140,000. Further, we suspect that many patients remain undiagnosed. In our experience, symptoms start during childhood, notably in physical education classes. However, diagnosis was delayed until older ages in 96% of the Spanish patients. There is large individual variability in clinical severity and some patients have intolerance only to strenuous exercise or sport activities.\(^{(25)}\) Since ~1/3 of adult westerners are inactive (performing less than 150min/week of moderate PA \((16)\)) and many do not practice any strenuous sport activity, it is not unreasonable to suspect that some cases remain unnoticed.

In the Spanish patients there is no \textit{PYGM} genotype-phenotype correlation despite the large heterogeneity commonly reported in disease severity. Some patients (~8%) are virtually asymptomatic during activities of daily living but many more (~50%) are limited even during daily life (including personal care or household tasks). In addition, the commonest nonsense p.R50X mutation (resulting in NMD and thus in null myophosphorylase activity) is also present among the less affected patients. Patients’ PA habits explain the individual variability in the phenotype manifestation of myophosphorylase deficiency. The majority (81%) of physically active patients \(\textit{ie},\)
those whose levels of moderate PA were above the minimum threshold of 150min/week according to both the 2011 US guidelines published by the American College of Sports Medicine and the 2011 UK Government, [33]) moved to a lower severity class in just 4 years. In fact, active patients are usually found in the lower severity class of the clinical classification -that is, having intolerance only to strenuous exercise and showing no limitation during activities of daily living. Furthermore, PA is positively associated with a key healthy indicator, cardiorespiratory fitness (determined as peak oxygen uptake, \(\text{VO}_{2}\text{peak}\)). This is an important consideration because the \(\text{VO}_{2}\text{peak}\) of many patients, especially women, barely reaches the limit (~4 metabolic equivalents, METs) necessary for independent living. However, some physically active patients have a \(\text{VO}_{2}\text{peak}\) level \(\geq 8\) METs, which is the minimum threshold for optimal health in middle-aged adults (20)). One active patient even reached \(~11\) METs (which reflects an optimum cardiometabolic profile (4)) despite having, like the rest of Spanish patients, no myophosphorylase activity in his muscle. Thus, the beneficial muscle biological adaptations to regular PA (increased OXPHOS capacity or muscle mass and power, among others) are likely to compensate, at least during non-strenuous activities, for the inherited blockade in glycogenolysis.

Some recent initiatives are helping to increase the knowledge on McArdle disease, notably the EUROMAC project, the aim of which is to register all European patients (http://www.patient.co.uk/health/media/videos/mcardle-s-disease-and-euromac-registration).

Other potential, \textit{PYGM}-independent genotype modulators of the disease phenotype

The two genetic polymorphisms that have been more widely studied in exercise sciences owing to their potential impact on some muscle-related phenotypes such as sprint/power (10) or endurance sports performance (11), \textit{ie}, the 287bp insertion(I)/deletion(D) polymorphism [rs1799752] of the angiotensin converting enzyme (\textit{ACE}) gene and the p.R577X (p.Arg577*) polymorphism (rs1815739) of the \(\alpha\)-actinin-3 gene (\textit{ACTN3}), can potentially modulate McArdle disease severity. The \textit{ACE} I-allele, which is theoretically associated with lower enzyme activity, improved cardiovascular function and higher uptake of blood glucose into skeletal muscle fibres,(60) favors a less severe clinical presentation (28, 44) as well as higher \(\text{VO}_{2}\text{peak}\) in
McArdle patients compared with the D-allele. A 12-week treatment with the ACE inhibitor ramipril (2.5 mg/day) improved VO$_{2\text{peak}}$ in D/D patients. Women who were diagnosed with McArdle disease, carriers of the ACTN3 X-allele, had a higher VO$_{2\text{peak}}$ than their R/R counterparts. Finally, the coexistence in the same individual of McArdle disease and homozygosity or even heterozygosity for the mutant allele of the C34T (Glu12Stop) nonsense mutation in the gene encoding muscle adenylate deaminase (AMPD1), an important regulator of muscle metabolism during intense exercise, might account for a more-severe phenotypic manifestation of the disease. Further research might identify other genetic variants that have an impact on exercise intolerance in these patients.

**Possible therapeutic interventions**

**Pharmacological/nutritional interventions.** In general, no major benefits have been shown when administering branched chain amino acids, depot glucagon, dantrolene sodium, verapamil, vitamin B6, D-ribose or creatine supplementation. Research with ‘modern’ molecular therapies aiming to up-regulate the expression of brain/liver isoforms in patients’ muscle (eg, valproic acid) or to restore, at least partially, myophosphorylase activity through gene therapy is underway and in fact some preliminary data are already available. However, a successful outcome of these valuable efforts might not be seen in the foreseeable future (see (37) for a review). In contrast, simple carbohydrate-based nutritional interventions have proved beneficial to the physical performance of patients and to attenuate exercise intolerance. Drinking 660 ml of a beverage with 75 g of sucrose some 40 minutes before exercise abolished the second wind phenomenon and improved aerobic power. A beneficial, more sustained effect on exercise capacity was obtained by the same group after oral ingestion of a lower dose (37 g) of sucrose, shortly (5 minutes) before the exercise. A carbohydrate-rich diet improved maximal power output during a gradual cycle-ergometer test by 25% compared to the protein-rich diet. The abovementioned effects were attributed to higher hepatic glycogen stores in the patients (in the case of dietary manipulation) or directly to higher glycaemia (in the case of pre-exercise ingestion of sucrose), leading in both cases to greater availability of glucose to the working muscles.
Physical activity interventions. The classical treatment recommendation is to be sedentary but this may further exacerbate the condition: serum CK levels are more elevated in inactive patients(25) and rhabdomyolysis has been reported to persist even following a 20-year period of inactivity.(39) Inactivity may also restrict muscle ability to metabolize alternative fuels to bypass the block in glycogen metabolism. In fact, transcriptomic studies have shown that, compared to healthy controls, patients’ muscles have lower expression of proteins involved in muscle metabolism and Ca\(^{2+}\) homeostasis.(34) Also, by avoiding exercise, McArdle patients are susceptible to secondary health risks such as type II diabetes and cardiovascular disease.(31)

In 2005, the first study (38) was published showing the benefits of supervised ‘aerobic’ exercise interventions in McArdle disease. Five patients were trained on a cycle-ergometer at 60-70% of their maximum heart rate 3 times a week (45 minutes/session) during 8 weeks. After the training period, they showed attenuated exercise intolerance with earlier appearance of the second wind. The second article was published in 2006 (2) reporting the training effects in 8 patients (4 male and 4 female). They were also trained on a cycle-ergometer for 14 weeks [frequency: 4 times/week; intensity: 60-70% of maximum HR; sessions’ duration: 30 (start of the program) to 60 minutes (at the end)]. Patients increased values of peak work capacity (watts), VO\(_{2}\)peak and cardiac output and some key enzymes of mitochondrial metabolism post-exercise training compared to baseline. In 2007, our group reported training effects in 9 patients.(29) They walked or trained on a cycle-ergometer (5 sessions/week) for 8 months. Intensities and duration of sessions were similar to the aforementioned studies. They ingested 100 g of complex carbohydrates one hour before exercise, and consumed a sports drink (330 ml, equivalent to 30 g of simple carbohydrates) 5 minutes before exercising (see above for the rationale of these nutritional recommendations). Several indicators of exercise capacity, including mainly VO\(_{2}\)peak, increased with training. The abovementioned interventions were proven to be safe, since no health risks were reported due to the exercise sessions.(42) In fact, we observed a reduction in serum CK levels after training (29), suggesting that stimulation of muscle activity may counterbalance muscle damage and wasting,(24) by activating other pathways that may induce muscle repair.

The effects of carefully supervised and individualized resistance exercise (weight lifting) have also been assessed in an 15-year old male patient (13) and in 7 middle-aged patients of both genders.(47) The adolescent performed a 6-week, supervised, light to
moderate intensity program (~65-70% of one-repetition-maximum, 1RM; 2 sessions/week).(13) After the intervention his 1RM bench press and multi-power squat performance improved by ~27% and ~6% respectively. No myoglobinuria episodes were reported during the study. Further, the patient had moved to a lower disease severity class after training -that is, he became virtually asymptomatic in terms of exercise limitation.(13) Santalla et al. (47) recently reported, in 7 adult McArdle patients (5 female), the effects of a 4-month light-moderate circuit weight lifting training program (2 sessions/week) followed by a 2-month detraining period on the following variables: muscle mass (assessed by dual-energy X-ray absorptiometry) and muscle strength, serum CK, and clinical severity. No major contraindication was noted during the training intervention, which had a significant positive impact on total lean mass (which increased by nearly 1 kg) as well as on bench press and half-squat performance (an effect which was demonstrated in all the participants). All the patients improved with training as indicated by their subsequent condition being classified as less severe. The improvement was such that, following exercise intervention none of them were in the highest disease severity class anymore and, accordingly, they did not have fixed muscle weakness or limitations in daily life activities.

Conclusions and future directions: What can we learn from this disease?

McArdle disease represents a unique model and we can learn several useful lessons from it. Muscle glycogen is a crucial fuel, especially for intense exercise tasks, and ‘extreme’ dietary habits resulting in low stores might decrease adaptability to some challenging exercise interventions with increasing popularity, notably those based on ‘high intensity interval training’ (HIT). Besides decreasing performance, it is possible that performing HIT under conditions of low glycogen availability might increase, at least partly, the risk of rhabdomyolysis in the less adapted participants. Rhabdomyolysis is in fact a matter of growing concern in sports medicine, with numerous cases been reported in children (62) or in adults taking up a theoretically low-risk exercise program (ie, with little eccentric contraction component) such as indoor cycling.(18) In addition, an increasing number of westerners are under treatment with cholesterol-lowering drugs (statins), which are known to further increase the risk of exertional muscle damage.
Thus, *PYGM* genotyping should be maybe included in the genetic analyses that might be applied in the coming personalized exercise medicine. It might be also applied in future research on genetics and exercise-related phenotypes in order to indentify individuals who might be carriers of *PYGM* mutations (*ie*, heterozygous) and thus show some limitations in the capacity to perform intense exercise despite not having the disease itself (see below). It could be that some undiagnosed McArdle patients (or at least carriers of *PYGM* mutations) might be among the proportion of hypo-responders (or even among those showing some adverse responses in the form of muscle damage) to intense training interventions, *eg*, HIT. In this regard, the genetically-modified McArdle mouse model recently generated by our group might help gain insight on the ‘pathogenomics’ of exercise intolerance and rhabdomyolysis. Despite retaining ~50% of normal myophosphorylase activity and still performing considerably better than McArdle (p.R50X/p.R50X) mice, the exercise performance of heterozygous mice was lower than normal (-12%) in treadmill tests and some of them showed very poor (‘McArdle-like’) performance in the wire grip tests.(36) This finding reflects the importance of retaining virtually 100% of myophosphorylase function for ensuring normal levels of maximal exercise capacity, despite the fact that humans who are heterozygous for pathogenic *PYGM* mutations are thought to be free of major disease symptoms during daily life activities.(1) Importantly, De Castro et al have recently estimated that the prevalence of carriers of *PYGM* pathogenic mutations is not negligible, *ie*, one every 63 people.(8)

Another unresolved question is the functional consequence of *PYGM* polymorphisms: 42 different polymorphisms, with a minor allele frequency ≥1% have been described in the *PYGM* gene, and, although the majority of them are intronic some exonic variants deserve study, notably the one found in the 5’UTR of the exon 1 sequence (rs483962) (see (33) for a review). Indeed, *PYGM* genotype might be among the muscle-specific metabolic gene modulators explaining individual variability in human exercise responses and adaptations as well as in sports performance. Another candidate muscle-specific genotype that is seldom accounted for in exercise studies is the T/T genotype for the abovementioned C34T mutation in *AMPD1* gene. The T/T genotype (with a population frequency ~1-2%) is associated, like McArdle disease, with decreased tolerance to intense exercise since childhood, in the form of unpleasant cramps or weakness (12). In fact, this genotype is among those that were associated with
individual variability of human responses and adaptations to exercise in the prestigious HERITAGE study.(43)

Finally, regular, moderate-intensity PA reduces the severity of McArdle disease. The results of previous research exemplify the feasibility and benefits of personalized, professionally supervised exercise programs: light-moderate intensity exercise (especially if preceded by carbohydrate ingestion) is currently the only useful therapy for this disorder. In contrast, HIT or other intense programs with increasing popularity are to be discouraged in this and other diseases that are associated with exercise intolerance.

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LEGENDS TO FIGURES

Figure 1. Skeletal-muscle glycogen metabolism and main glycogen storage diseases (GSD) due to specific enzymatic defects. Of note, because in Mc Ardle disease the metabolic blockade occurs in the first step of glycogen metabolism (i.e., upstream the uptake of blood glucose by muscle fibres), blood glucose can enter the muscle fibres where it is converted into glucose-6-phosphate. Thus, at least partially, the defect in glycogen metabolism can be attenuated by ensuring high availability of blood glucose to working fibres before/during exercise (see text). This is in contrast with the other types of GSD.

Figure 2. The ‘second wind’ phenomenon and main hypotheses on the pathophysiology of McArdle disease (especially regarding exercise intolerance, which is most marked before the second wind). The second wind is easy to identify during constant load (~40 watts for most adult patients) cycle exercise eliciting a heart rate value of 60-70% of the predicted maximum heart rate (i.e., 220 beats·min⁻¹ minus age in years): patients typically show a decrease in early exertional tachycardia after 7-10 minutes. Dotted lines denote the consequence of complete inability for glycogen use and red arrows denote ‘down-regulation’. Abbreviations: OXPHOS, oxidative phosphorylation SERCA1, sarcoplasmic reticulum Ca²⁺ ATPase (SERCA).

REFERENCES


**Figure 1**

Diagram showing the process of glycolysis and its relation to different muscle fiber types and conditions such as phosphofructokinase deficiency (GSD VII, Tauri Disease) and lactate dehydrogenase deficiency (GSD XI). The diagram also illustrates the conversion of glucose to pyruvate, which can enter the mitochondrial matrix for aerobic metabolism or be converted to lactate during anaerobic glycolysis.
Figure 2

Heart rate (beats ·min⁻¹)

Marked exercise intolerance (muscle pain, contractures)

Improved muscle function

Second Wind

Hyperkalemia and decreased membrane excitability

Glycogen overload, blocked glycolysis and substrate deficit in oxidative phosphorylation

Slowing of relaxation and impairment of excitation-contraction-relaxation coupling

Improved muscle function