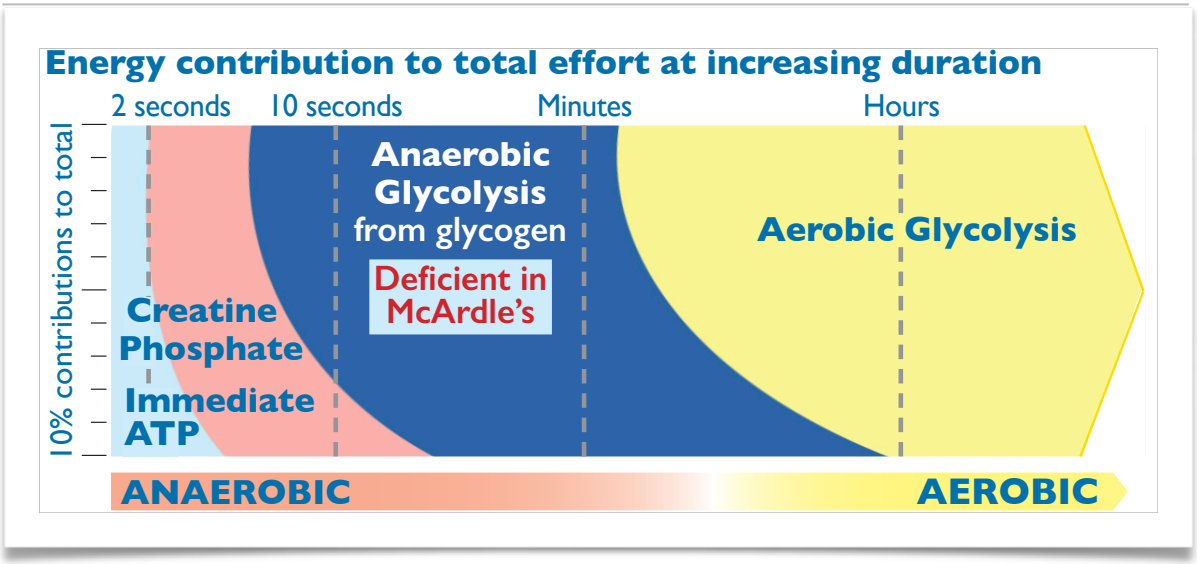
Appendix 3

Physical Training Guidelines

Aerobic and resistance training

The energy crisis in GSD V and GSD VII

The muscle glycogen storage diseases McArdle disease (GSD V) and Tarui disease (GSD VII) are rare metabolic myopathies caused by homozygous or compound heterozygous mutations in the *PYGM* and *PFKM* genes, respectively. In GSD V a lack of the enzyme myophosphorylase results in impairment of muscle glycogen breakdown (glycogenolysis), and in GSD VII there is a complete block in glycolysis in the muscle due to deficiency of the enzyme phosphofructokinase; both of these disorders result in a distinct energy crisis in skeletal muscle metabolism [3].



Schematic representation of the percentage contribution of main energy sources for skeletal muscles during activity. The blue section represents the affected glycolytic system (glycogen) in patients with McArdle disease.

The primary issue for individuals with GSD V or GSD VII is managing muscle energy in order to lessen muscle fatigue, cramping, and pain during activities of daily living (ADL) and formal exercise. If physical activity is continued in spite of these symptoms, muscle damage may ensue, with the risk of exertional rhabdomyolysis, contracture and related adverse events.

Exercise with GSD V and GSD VII

Moderate aerobic exercise interventions for people with GSD V or GSD VII are beneficial and safe, and will improve aerobic endurance [4]. However, there are some rules to follow within the type of training.

- Patients with GSD V have severely limited adenosine-5′-triphosphate (ATP) resynthesis due to both the absence of glycogenolysis and limited mitochondrial oxidative phosphorylation because of reduced substrate availability.
- Patients with GSD VII cannot catalyse the conversion of fructose 6-phosphate to fructose 1,6-bisphosphate; accordingly, the use of both muscle glycogen and blood glucose is blocked.

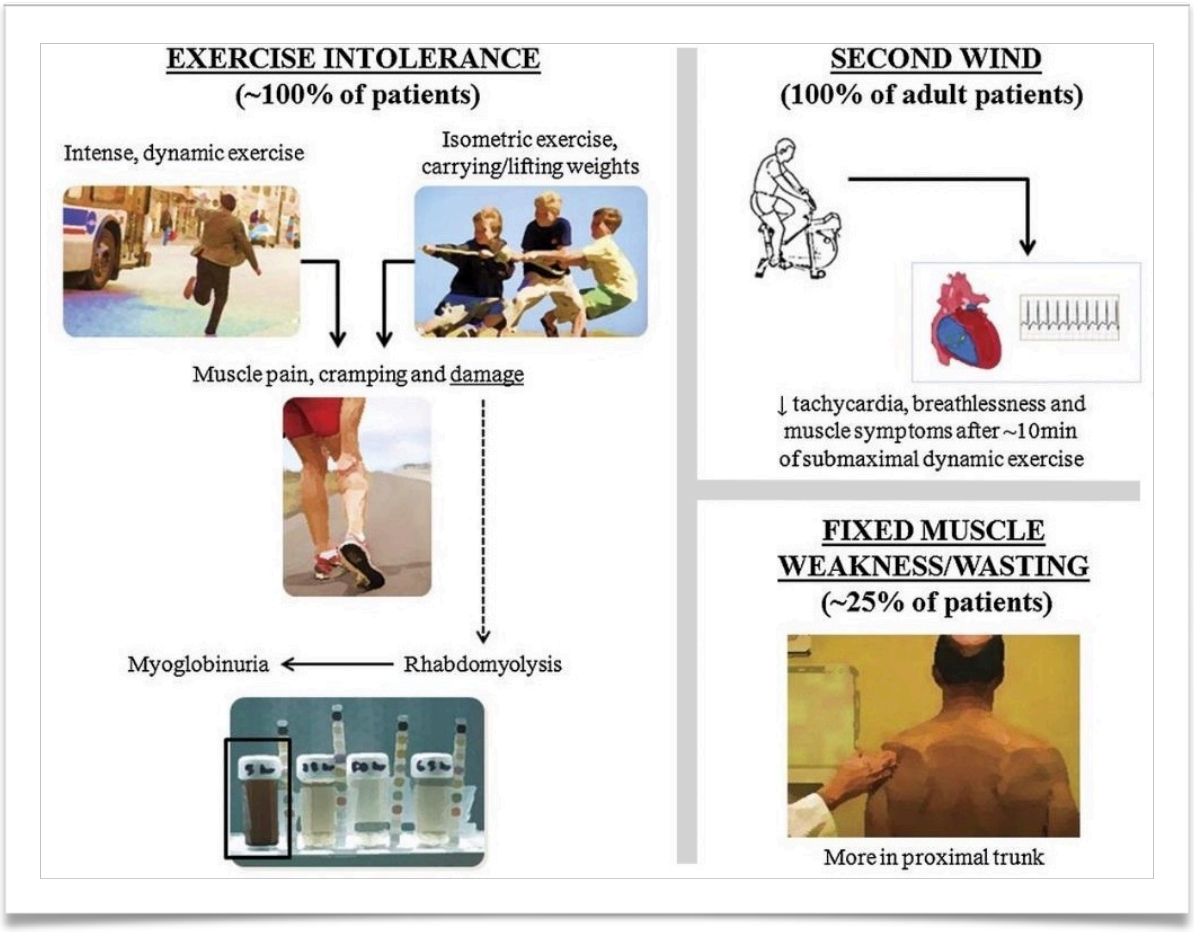
Thus, the exercise intolerance in patients with GSD V or GSD VII is caused by an imbalance between muscle energy demand and supply [3]. During high intensity aerobic and all anaerobic exercise, skeletal muscle is dependent upon glycolysis for energy. Hence, in these patients during short-term moderate-to-vigorous physical exertion, requiring anaerobic metabolism and a high glycolytic flux for oxidative combustion, an acute energy crisis occurs. Within the first minutes of exercise, and with increased intensity of ongoing exercise, unpleasant symptoms occur, which include tachycardia, severe muscle pain and fatigue. If exercise continues at the same intensity despite these symptoms, a muscle cramp occurs. This can result in severe muscle damage (rhabdomyolysis), leading to a contracture involving muscle tenderness, swelling and weakness. Rhabdomyolysis leads to the release of the muscle protein myoglobin, which is excreted through the kidneys, causing a reddish-brown discoloration of urine known as myoglobinuria. This can lead to acute renal failure, which may require dialysis and intensive care to reverse [4].

Patients with GSD V experience a ‘second-wind’, which is not shown to occur in those with GSD VII. If physical activity continues in a gentle manner, with the patient repeatedly slowing down or pausing when symptomatic, and then resuming activity once asymptomatic, after approximately 8-10 minutes the ‘second-wind’ phenomenon will occur. At this time symptoms will begin to subside and physical activity can be pursued more freely [6–9]. ‘Second-wind’ in GSD V occurs due to a change in the balance of muscle energy metabolism away from glycolysis and towards oxidative phosphorylation. This happens because of increased blood flow in the skeletal muscle, which enables the body to use alternative sources of energy (aerobic metabolism), such as glucose released from the liver glycogen store, and fatty acids, carbohydrate, and protein metabolism via mitochondrial respiration [6,10]. This metabolic shift enables individuals with GSD V to engage in submaximal physical activity with more normal muscle functioning.

Physical activity in daily life

In GSD V ‘second-wind’ is a useful tool that enables individuals to engage in activity/ exercise with greater ease. However, this does not apply in GSD VII. The 8-10 minutes prior to achieving ‘second-wind’ presents a distinct challenge. Spontaneous movement is generally

required in day-to-day life to carry out various ADLs, from small tasks like opening a can of soup and washing hair, to bigger ones such as carrying groceries or housework. Because most ADLs do not last longer than 8–10 minutes, patients find themselves constantly struggling to manage their energy output throughout the day. As 'second-wind' is muscle specific and abates following periods when those muscles are not in use, the practicality of achieving 'second-wind' over and over throughout the course of a day is problematic. It is essential for patients to understand this.



Main clinical features of McArdle disease [14].

Physical exercise training

Because of the risk of rhabdomyolysis, training in patients with GSD V or GSD VII should, at least initially, take place under strict supervision. Patients with GSD V always need 5-10 minutes to get into their 'second-wind' and thus improve exercise tolerance and reduce the risk of rhabdomyolysis [8,11–13].

For patients with GSD V, *but not in those with GSD VII*, before warm-up, a glucose ingestion is recommended to ease transition into 'second-wind'. For this, drinking a can of a conventional isotonic drink (20–30 g of glucose) 5 min before beginning to exercise is suggested [14]. This is especially important for sedentary patients, whereas trained patients

will have developed lipid metabolism and will become less dependent on this pre-exercise glucose ingestion. This glucose ingestion is contraindicated in patients GSD VII, as patients are shown to experience an 'out-of-wind' phenomenon [15,16].

Anaerobic exercise or static muscle contractions (for example, isometric contractions for a long time, such as planking or wall sit) should be avoided. If a patient with GSD V or GSD VII starts his or her training too quickly or too intensely (anaerobic), there is a risk of rhabdomyolysis.

Aerobic training

The following guideline is established for patients with GSD V. Those with GSD VII may be able to carefully follow the same guideline, with the exception of 'second-wind', although the low incidence of GSD VII means there is insufficient evidence to recommend it.

Patients should start with a very light warm-up (for example, cycling at 30 RPM without resistance), during which the rating of perceived pain (RPP) should not exceed 3 (on a scale of 0 to 10, where 0 is no pain and 10 would be maximum pain). After achieving 'second-wind', moderate-intensity aerobic exercise applied gradually should help to improve muscle metabolism. During aerobic training (for example, brisk walking, cycling, swimming) the heart rate should ideally be between 50% and 75% of the maximum heart rate. The approximate maximum heart rate can be calculated using the Tanaka formula: $208 - (0.7 \times \text{age})$ [17]. Aerobic training intensity can also be controlled by a rating of perceived exertion (RPE), given the great sensitivity of muscle perception in these patients. Thus, 50–70% maximum heart rate is equivalent to an exercise intensity in which RPE is 5–7 (on a scale of 0 to 10, where 0 is no effort and 10 is maximum effort) with no pain, or at least minimal pain ($RPP \leq 1$). The frequency of training should be between 2 and 4 times a week, for a minimum of 20 minutes up to a maximum of 1.5 hours. Aerobic adaptations are important to improve submaximal physical activity tolerance [13], and to ease the transition into 'second-wind' in ADLs (such as walking). In terms of adaptations, there is a dose effect; the more days and hours of aerobic training a week, the easier it will be to achieve 'second-wind' in ADLs. After a training session, light dynamic stretching and good hydration are recommended.

Resistance exercise

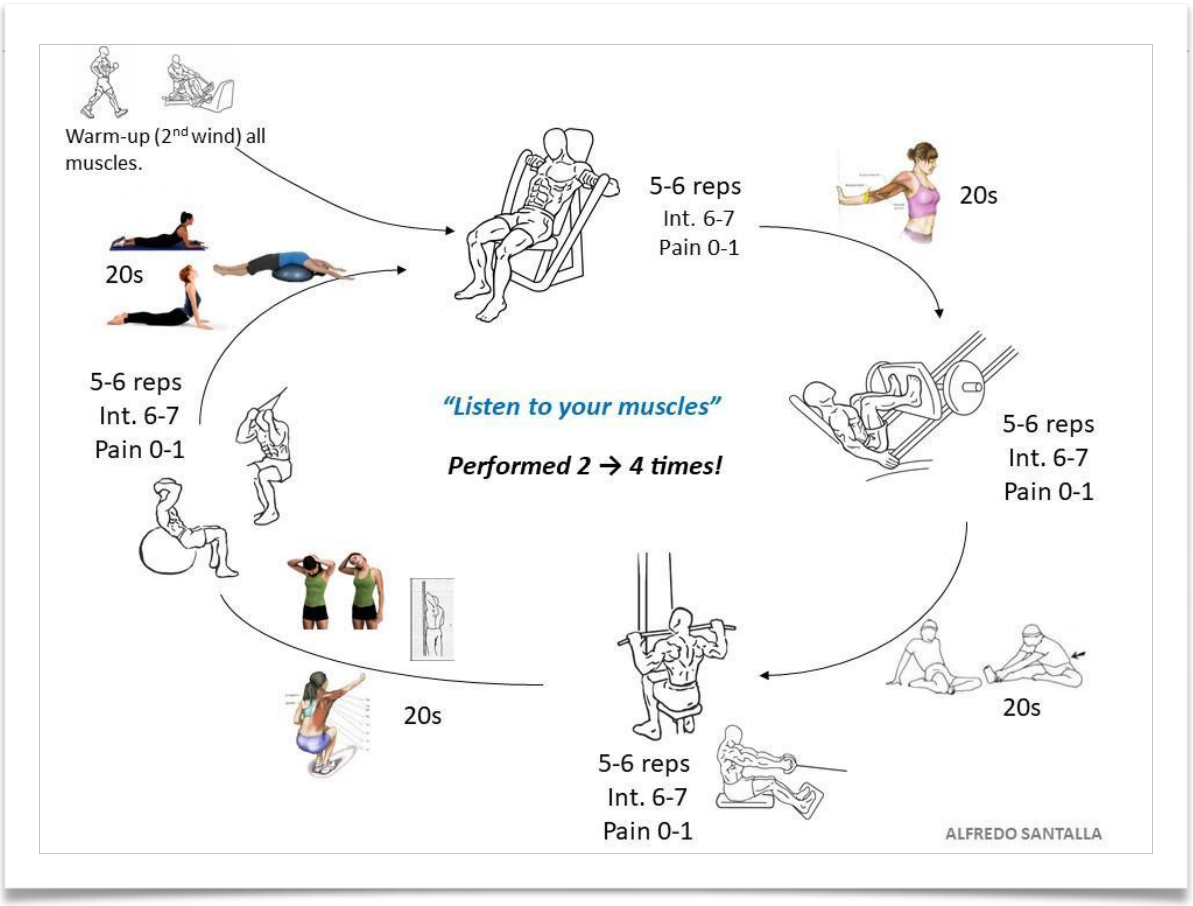
For GSD VII, the low incidence means that there is not adequate clinical data to recommend strength training.

Strength training in patients with GSD V should be carried out on 2–3 non-consecutive days per week to achieve training adaptations (increase in muscle mass, changes to a lower severity class, decrease in baseline CK and absence of fixed muscle weakness) and must meet certain guidelines to avoid risk of contractures or rhabdomyolysis [3,18,19].

In addition to glycogen, another short burst of energy for high intensity exercise is provided via the phosphagen pathway (ATP–phosphocreatine system). This allows for anaerobic activities lasting up to 10 seconds at maximal exercise intensity [20,21]. The more

intense the exercise is, the faster the energy is consumed from the ATP–phosphocreatine system. It takes around 3 minutes to fully replenish this energy source [19]. As this metabolic pathway is not impaired in GSD V, patients may exercise safely when keeping within the ~10 seconds of energy availability [3]. Therefore, for resistance or strength exercise, the 6-second rule applies; power efforts should not last longer than 6 seconds. After that, the creatine phosphate pool may become empty and the patient cannot switch to anaerobic metabolism.

The ideal strength session structure would be:



Structure of a strength training session. Adapted from [19].

Warm-up: First, a small intake (~20–30 g) of simple carbohydrate (330 ml of conventional isotonic drink) [8,14] to improve glucose flow to the muscle. After 10–15 minutes walk/pedal for 12 minutes and then do 12 minutes of exercise in an arm-crank ergometer. This approach will trigger the occurrence of the 'second-wind' in both upper and lower body muscles.

Strength training: Strength training must be carried out using equipment to exercise large muscle groups [18,19]. Sets of 6 repetitions are recommended to avoid depletion of the phosphagen deposits (and therefore avoid muscular crisis) [18,19]. It is recommended to gently stretch for 10–30 seconds after each set, to reduce stiffness [3,18,19]. It is important to follow a circuit training structure, rotating on multiple equipment to give a recovery time of

at least 3 minutes between sets, to facilitate phosphagen resynthesis. As an example, a typical strength training session would be to perform 3 to 4 turns to a circuit: Leg Press → Chest Press → Seated Rowing or Lat Pull Down → Abdominal Machine [18]. The load (kg) on each equipment should be set to elicit an RPE of 6-7 and an RPP of 0–1 (both on scales of 0–10) at the end of the set. Load (kg) can be increased when RPE remains below 6 for two consecutive sessions. In the event of perceiving pain rising quickly it is important to stop the exercise, or risk contracture. When resting, it is recommended to undertake dynamic movements (without load) and gentle stretching until this perception disappears and then to continue the circuit.

Cool-down: It is recommended to undertake low intensity dynamic exercise (for example, pedalling or walking) and to end the session by doing a global passive stretching routine and to hydrate with plain water [19].

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