Title: Exercise and pre-exercise nutrition as treatment for McArdle disease

Short running title: Exercise in McArdle disease.

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ABSTRACT

McArdle disease is due to an inborn defect in the muscle isoform of glycogen phosphorylase (or 'myophosphorylase'), the enzyme that catalyses the first step of glycogenolysis. This condition is still not fully understood and, while advances in research would help patients immeasurably, these would also enhance our understanding of exercise metabolism. It has been ten years since the first published report demonstrating the benefits of regular aerobic exercise for these patients. However, misconceptions remain and the value of exercise prescription for McArdle patients is still underlooked. Here we review the role of exercise in McArdle disease with the aim to better inform healthcare professionals and thus better serve the interests of patients. Recommendations for regular exercise together with pre-exercise nutrition in children and adult patients are also provided along with examples of exercise practice and its benefits.

KEY WORDS

Glycogenosis type V, exercise therapy, training, dietary recommendations, active life-style

INTRODUCTION

Endogenous muscle glycogen is a primary source of energy during exercise, and a close relationship exists between this substrate reservoir and a person's capacity for intense endurance exercise (3, 13). The enzyme responsible for muscle glycogen catabolism during exercise is muscle glycogen phosphorylase (M-GP), which releases glucose-1-phosphate from glycogen. Glucose-1-phosphate then becomes available for glycolysis and subsequent oxidative phosphorylation or anaerobic utilization. In 1951, Dr. Brian McArdle (21) described a clinical condition in which the metabolism of muscle glycogen was impaired or blocked. Patients with this condition, known as 'McArdle disease' or 'glycogen storage disease' (or simply 'glycogenosis') type V (GSD5; MIM # 232600), show exercise intolerance as their main clinical symptom. Muscle biopsies in McArdle patients are characterized by glycogen storage deposits that these individuals are unable to metabolize (26). The study of McArdle disease has improved our knowledge of muscle metabolism specifically and exercise physiology in general.

One of the major metabolic sequelae of McArdle disease is an inability of working muscles to produce lactate during physical activity. In healthy individuals, blood lactate concentration rises with increasing exercise intensity. Lactate acts as an important fuel source directly through its oxidization in muscle (11), or indirectly, via the liver as a substrate for gluconeogenesis (7). Because lactic acid is a strong acid, lactic acid produced by contracting muscles dissociates into lactate and H^+ in aqueous solution, i.e., within muscle or blood (42). When the rate of demand for ATP outstrips its supply, predominantly by ß-oxidation, Krebs cycle and the electron transport chain, anaerobic glycolysis-derived lactate starts to accumulate in the blood. Such accumulated lactate was traditionally erroneously considered to contribute directly to the onset of muscle fatigue. However, as mentioned above, it is now known that lactate is a valuable precursor of carbohydrate. McArdle patients have normal resting blood

lactate values (usually≤1 mmol·l^{-1}) yet in response to an increasing exercise intensity, blood lactate concentrations fail to change or may even decrease (**Figure 1**). Further, the muscle oxidative capacity of McArdle patients is also usually impaired (6, 43): owing to blocked glycogenolysis, the ability of their muscles to produce pyruvate, a molecule that plays an anaplerotic role in the Krebs cycle, is greatly reduced (16). Impaired muscle oxidative capacity in these patients has been shown in research using phosphorus magnetic resonance spectroscopy (31P-MRS) (43). Because of the abovementioned decrease in oxidative phosphorylation capacity, inorganic phosphate (P_i) accumulates in patients' muscles, with the latter being a major cause of fatigue during exertion (42). Indeed, accumulation of P_i can potentially inhibit the myofibrillar ATP-ase, and might also alter Ca^{2+} handling in the sarcoplasmic reticulum as well as the Na+–K^+ ATP-ase reaction in the sarcolemma, leading to decreased contractility and premature fatigue (12, 15).

WHAT IS McARDLE DISEASE?

McArdle disease is an autosomal recessive disorder caused by mutations in the *PYGM* gene (MIM # 608455), which codifies M-GP. Only M-GP is expressed in skeletal-muscle tissue as opposed to the two other isoenzymes, which are encoded by *PYGL* (liver isoform) and *PYGB* (brain) gene. Thus, McArdle disease is a 'pure' myopathy that only affects the skeletal muscle. To date, 147 different mutations giving rise to the disease have been described in this gene (24). However, genetic heterogeneity does not follow any genotype-phenotype correlation (18, 39), since the vast majority of patients show null M-GP activity upon muscle biopsy (5, 25). The prevalence of McArdle disease is thought to be largely underestimated in American (5, 25) and in Spanish population (5, 25), and could be in the range of 1:50,000 to 1:200,000. Although classified as a rare disease (ORPHA368), it is the most common muscle glycogen storage disease or 'glycogenosis'.

Classically, the disease has been described as presenting with broad clinical heterogeneity. McArdle patients are classified into four classes using a phenotypic scale (19): class 0, asymptomatic or paucisymptomatic (mild exercise intolerance, with no limitation in daily activities; class 1, classical presentation including exercise intolerance, recurrent cramps, myalgia and limitations in daily activities, but with no myoglobinuria or muscle weakness; class 2, classical presentation with myoglobinuria; and class 3, classical presentation with myoglobinuria and fixed muscle weakness, severely limiting daily activities.

Cohort studies have shown that despite clinical heterogeneity, some main clinical features are common to the majority of patients. These include a history of acute exercise intolerance crises when performing intense dynamic or isometric exercises. Among those patients 50% have recurrent episodes of dark urine or myoglobinuria (18). Muscle pain is mainly restricted to muscles involved in locomotion and postural control (28). Another prevalent feature is the presence of high baseline levels of a marker of skeletal muscle damage, serum creatine-kinase (CK) activity, i.e., well above 200 $U \cdot l^{-1}$ in most patients and > 1,000 $U \cdot l^{-1}$ in 80% (18, 39). Lastly, a frequent characteristic is the report by most patients that they experience a 'second wind', that is, attenuation in exercise intolerance after ~7-10 minutes of dynamic exercise (e.g., brisk walking). This 'sign' is characterized by reduced or absent muscle pain, and both a slower breathing rate and heart rate following their increase at the start of exercise (18).

Other characteristics of the disease are that 25% of patients (clinically classified in the highest severity, class 3) develop fixed muscle weakness and wasting affecting mostly proximal trunk muscle groups. In rare cases, patients are paucisymptomatic (18, 39) and occasionally diagnosed by another affected individual (indicating intra-familiar clinical heterogeneity). Acute renal failure is infrequent, e.g., only shown by 4% of patients in the Spanish registry (18), although an incidence of 11% has been reported in UK patients (34). Additionally,

localized muscle atrophy is detected in a small number of patients (39). In general, McArdle's symptoms are aggravated as patients' age (23, 39).

The main clinical features of the disease are summarized in **Figure 2.**

DIAGNOSIS PAYING PARTICULAR ATTENTION TO CHILDREN

Diagnosis should be made as early as possible since this will improve patient management. Some of the disease's features are unique to this condition and should facilitate diagnosis in adult patients: history of exercise intolerance, high resting serum-CK levels and the 'second wind' sign. Clinicians should pay special attention to the later sign since it is pathognomonic for the disease. It can easily be confirmed in a 15-minute cycle-ergometer test at low constant workload (e.g., 40 watts) while monitoring heart rate (40).

Since disease onset in approximately 60% occurs in the first decade of life and in 28% in the second decade of life (18, 28, 39), it is especially important that pediatricians are aware of the disease. Diagnosing McArdle disease in children is particularly challenging because metabolism and exercise patterns differ compared with adults. Short, discontinuous bouts of exercise typical of children with McArdle's makes the 'second wind' less detectable at very young ages (33). In very young patients, suspicion of McArdle disease should be prompted by elevated serum-CK, and self- or parent-reported problems such as undue fatigue and muscle pain during physical education classes or when playing in the school playground. Pre-school children may be late to walk and 'bottom shuffling' is more common than crawling. At this age, children with the disease may also seek to be carried more frequently.

Genetic testing is clearly the best diagnostic tool for McArdle disease. The prevalence of certain *PYGM* gene mutations varies such that mutations described as being more common in the literature should be tested for first. This approach can accelerate the genetic diagnosis since complete *PYGM* gene screening involves the study of 20 exons (24). A proposed procedure

described for the Spanish population as a flowchart allows the identification of 75% of *PYGM* mutations in a fast and cost effective manner (37). A muscle biopsy is only recommended when *PYGM* gene sequencing returns no mutations. These cases are extremely rare, and their diagnosis requires muscle biochemical tests and mutations need to be identified indirectly in muscle RNA (10).

TRADITIONAL APPROACH TO TREATMENT

As mentioned previously, in the past patients were recommended to refrain from any type of exercise, essentially because clinicians were concerned about the risk of rhabdomyolysis. Muscle crises in patients are usually triggered by acute bouts of intense exercise requiring the recruitment of a large volume of muscle mass (e.g., running for the bus) or by static contractions relying on small muscle groups (e.g., carrying weight). However, regular moderate-intensity aerobic exercise applied gradually and accompanied by dietary recommendations should help improve muscle metabolism (20, 35). Contrary to traditional advice, it has been reported that 50% of patients do not have a strictly inactive lifestyle (28). Despite this, however, McArdle patients usually have low aerobic power compared with their age- and sex- matched healthy peers (22), and only 3% of adult patients are able to fulfil the minimal threshold of peak oxygen uptake (VO_{2peak}) for optimal health, i.e., 8 metabolic equivalents (MET), or 28 $ml \cdot kg^{-1} \cdot min^{-1}$ (14).

Sedentary habits do not improve the clinical condition or attenuate the progression of muscle damage, with inactive patients showing greater increases in serum-CK levels (18). Rhabdomyolysis seems to persist even following a 20-year period of inactivity (32). Older McArdle patients are also more susceptible, by virtue of avoiding exercise, to secondary health risks such as type II diabetes and heart disease (22). These secondary health risks may be

avoidable, as a good level of physical conditioning has been linked to reduced risks of all-cause morbidity and mortality in the general population (4).

EXERCISE AS THERAPY

The first study (27) to address this issue in five male McArdle patients was published in 2005. Patients were trained on a cycle-ergometer at 60-70% of their maximal heart rate three times a week (45 minutes/session) for a total of eight weeks. After this training programme, patients showed improved exercise intolerance including the earlier onset of the second wind. In a second article published in 2006 (1), training effects were assessed in four men and four women with McArdle disease. Patients were also trained on a cycle-ergometer, this time, four times a week for 14 weeks. Exercise intensity was 60-70% of their maximal heart rate and the duration of the sessions was increased from 30 minutes during the first half of the programme to 40 minutes thereafter. Compared to baseline, patients showed higher values of peak work capacity (watts), VO_{2peak} and cardiac output after the training programme. Additionally, training induced increased levels of key mitochondrial metabolism enzymes, indicating improved muscle oxidative capacity. In 2007, our group reported training effects in nine patients with McArdle disease (20). Patients either walked or trained on a cycle-ergometer five times per week for eight months. Intensities and session duration were similar to the aforementioned studies, though patients ingested 100 g of complex carbohydrates one hour before exercise, and drank a sports drink (330 ml, equivalent to 30 g of simple carbohydrates) five minutes before exercise (see below for explanations of these nutritional recommendations). Several indicators of exercise capacity, notably ventilatory threshold and VO_{2peak}, improved with training.

The above studies reported that exercise interventions were beneficial and safe, since no adverse effects of the training programmes were observed (36). Further, in the longer of the three studies (20), reductions in serum-CK levels were reported after training, consistent with

observations described in case reports of a child (29) and an adult patient (32). Hence, by stimulating muscle activity, muscle damage and wasting may be offset (16), possibly via the activation of muscle repair pathways.

In parallel with exercise programmes, some nutrition interventions have proved beneficial to the patients' exercise capacity. In 2003, a study showed that ingestion of a 660 ml drink with 75 g of sucrose ~40 minutes before start exercise abolished the second wind phenomenon and improved aerobic capacity (41). Concerned about the health effects of a high calorie intake in the form of simple carbohydrates, this same group performed a second study (1), in which a more sustained beneficial effect on exercise performance was observed after drinking a beverage with a lower dose (37 g) of sucrose only five minutes before exercise. Lastly in 2008, Andersen and Vissing compared the effect of a carbohydrate-rich *vs.* a protein-rich diet on patients' exercise capacity (2). Results indicated a 25% higher improvement in the maximal power output reached during a gradual cycle-ergometer test with the carbohydrate-rich diet. The benefits of the carbohydrate-rich diet would be attributable to higher liver glycogen stores leading to the greater mobilization of glucose during exercise that is thus available to the exercising muscles. For a complete review of all nutritional recommendations tested in McArdle patients see (35).

Exercise appears to be the main modifier of the clinical course of McArdle disease. Over a four-year period, 81% of physically active patients (i.e., physical activity levels above the minimum recommendation of 150 min/week according to US and UK guidelines published by the American College of Sports Medicine and UK Government in 2011, (8)) changed to a lower disease severity class (18). Patients who commit to a supervised, gradual exercise programme are able to improve their fitness levels almost as effectively as healthy individuals. Results are so outstanding that they become virtually asymptomatic during daily living activities (29, 32). In effect, active patients are usually assigned to the lower (='0') clinical severity class (18, 28).

It should also be noted that physical activity in general has been associated with improvements in VO_{2peak}; an important health indicator (4, 18).

WHAT SHOULD PATIENTS DO?

Although molecular/gene therapy studies designed to restore muscle M-GP activity (e.g., valproic acid therapy, enzyme replacement) in McArdle patients are underway, such valuable efforts are still far from obtaining translatable results. Regular physical activity is currently considered the best therapy for patients. The benefits of professionally supervised exercise programmes are their safety and ease of application. Although McArdle disease patients adapt well to regular exercise, training should be carefully designed to ensure a gradual progression of exercise intensity especially in the more severely affected patients (classes '2' and '3'). Under these premises, clinicians should encourage patients to adopt an active rather than a sedentary lifestyle.

In those taking up exercise, a carbohydrate drink before the first sessions is probably a prudent choice because it attenuates muscle pain in the first few minutes of exercise before the second wind (41) (see **Figure 3** for dietary recommendations) and thus help overcome a patient's fear of exercise (16). Metabolically this second wind can be explained by impaired glycogenolysis yet normal blood borne glucose metabolism, determining that blood glucose is an important fuel source in these patients. Thus, by ingesting glucose there is a modest increase in carbohydrate available in the first minutes of exercise, when muscle metabolism is more compromised (28) and so patients can better cope with hard physical tasks (35). Another recommendation would be a high-complex carbohydrate (65%), low-fat (20%) diet (2). This type of diet confers muscle protection during daily physical activities by ensuring a constant day-time supply of blood glucose. As with any exercise patients are recommended stretching their muscles before and after exercise, and drink abundant water after the exercise session.

Patients are recommended to choose a type of exercise they find enjoyable to maximize their commitment to regular exercise (for some guidelines, see **Table 1**). We also recommend that patients consult their physician to monitor the outcome of the training programme and a fitness professional to perform the necessary adjustments as fitness levels gradually improve. For children with McArdle disease, it is important to provide parents, caregivers and educators (especially physical education teachers) with appropriate information to ensure their best possible management. Children are the best candidates for exercise interventions, as healthy lifestyle habits are mainly adopted at very young ages (4-7 years), outdoor physical activities are usually a component of a child's daily routine and young muscles are especially trainable. Another important factor is that if patients become aware of their condition early on this will encourage them to accordingly adapt their lifestyle as soon as possible (22).

Trained patients can engage in vigorous dynamic exercise (17). Some patients have even shown great physical achievements (even compared with healthy people) including running a 10 km race in ~60 minutes (the average time for recreational runners (joggers) to complete 10 km is generally 75 to 80 minutes), climbing Kilimanjaro (5895 m), completing a 32 day-hike in the Welsh mountains (340 km) or obtaining a blue belt in Kajukenbo (http://blogs.bmj.com/bjsm/2012/11/26/mcardle-olympians-lessons-from-patients-own-experiences/).

HOW PATIENTS ADAPT TO REGULAR EXERCISE

When embarking on a regular exercise program, patients often report an improved sense of well-being and improved ability to perform activities of daily living, irrespective of their age (30, 31). To date, the McArdle disease patient followed-up for longest after aerobic training is a 9-year-old boy (29). At one-year of follow up, the child could keep up with his classmates in most physical activities and was virtually asymptomatic in physical education classes.

The effects of supervised resistance exercise have been assessed in a 15-year adolescent (9) and in seven middle-aged adults of both sexes (38). The adolescent undertook a 6-week, supervised, weight lifting program of light to moderate intensity (~65-70% of one-repetition-maximum (1RM); two sessions/week) (9) and followed the dietary recommendations detailed in **Figure 3**. After training, his bench press maximal strength (1RM) and multi-power squat performance increased by ~27% and ~6%, respectively. No myoglobinuria episodes were reported during or at the end of the programme and he was virtually asymptomatic after the training intervention (9). Santalla et al. (38) recently assessed the effects of a weight lifting training circuit programme of four-month duration and light-moderate intensity (two sessions/week) followed by a two-month detraining period in seven adult McArdle patients (five female) on: muscle mass assessed by dual-energy X-ray absorptiometry and muscle strength, as well as serum-CK and clinical severity. Again, no major adverse effects were reported with training, which induced significant increases in total lean mass (which increased by ~1 kg) as well as on performance in bench press and half-squat tests (observed in all participants). In response to training, disease severity decreased in all patients with no individual remaining in the highest disease severity class (='3') or showing fixed muscle weakness. Although resistance exercise seems particularly effective in McArdle patients, its implementation is not yet universal. This is because such physical training in this population requires substantial investment in qualified fitness professionals trained in managing this disease. Thus, unless training sessions are supervised by such experts, resistance exercise training is not recommended.

CONCLUSIONS

The acute and chronic beneficial effects of exercise in McArdle patients need further elucidation in adequately powered randomised controlled clinical trials. For the time being, simple healthy lifestyle interventions (good nutrition and regular exercise) are the most powerful strategy to combat exercise intolerance in these patients, the key being a pro-active attitude of clinicians, exercise professionals and patient associations.

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CONFLICT OF INTEREST

Authors declare no conflict of interest and that the present study do not constitute endorsement by ACSM.

LEGENDS TO FIGURES

Figure 1. Blood lactate response to a gradual dynamic exercise test (e.g., on a cycle-ergometer) in a McArdle patient vs. a healthy individual. Abbreviation: VO_2peak, peak oxygen uptake.

Figure 2. Main clinical features of McArdle disease. A. Main types of exercise that can induce exercise intolerance in patients. B. Schematic representation of the second wind phenomenon, a unique characteristic of the disease. C. Fixed muscle weakness.

Figure 3. Main pre-exercise nutrition recommendations for McArdle patients. *Not strictly needed, especially before light-moderate intensity activities or in fitter patients. Pre-exercise ingestion of simple carbohydrates in the form of sports drinks 'protects' muscles and considerably attenuates intolerance to strenuous exercise tasks during the first few minutes. This means it helps many patients overcome their fear of over-exertion.

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