Exercise and Preexercise Nutrition as Treatment for McArdle Disease

GISELA NOGALES-GADEA1, ALFREDO SANTALLA2,3, ALFONSINA BALLESTER-LOPEZ1, JOAQUÍN ARENAS3,4, MIGUEL ANGEL MARTÍN1,4,5, RICHARD GODFREY6, TOMÁS PINÓS5,7, GUILLAUME PINOS-MORELL1,8, JAUME COLL-CANTÍ1,9, and ALEJANDRO LUCIA3,10

1Translational Research Laboratory in Neuromuscular Diseases, Neurosciences Department, Germans Trias i Pujol Research Institute and Campus Can Ruti, Autonomous University of Barcelona, Badalona, SPAIN; 2Sports Sciences and Computing Department, Pablo de Olavide University, Sevilla, SPAIN; 12 de Octubre Hospital Research Institute (i + 12), Madrid, SPAIN; 3Mitochondrial and Neuromuscular Diseases Laboratory, 12 de Octubre Hospital, Madrid, SPAIN; 4Centre for Biomedical Network Research on Rare Diseases (CIBERER), Carlos III Health Institute, Madrid, SPAIN; 5Centre for Sports Medicine and Human Performance, Brunel University, London, UNITED KINGDOM; 6Neuromuscular and Mitochondrial Pathology Department, Vall d’Hebron University Hospital, Research Institute (VHIR), Autonomous University of Barcelona, Barcelona, SPAIN; 7Rare Diseases Unit, Pediatric Service, Germans Trias i Pujol University Hospital, Badalona, Barcelona, SPAIN; and 10School of Research and Doctorate Studies, European University, Madrid, SPAIN

ABSTRACT

NOGALES-GADEA, G., A. SANTALLA, A. BALLESTER-LOPEZ, J. ARENAS, M. A. MARTÍN, R. GODFREY, T. PINÓS, G. PINTOS-MORELL, J. COLL-CANTÍ, and A. LUCIA. Exercise and Preexercise Nutrition as Treatment for McArdle Disease. Med. Sci. Sports Exerc., Vol. 48, No. 4, pp. 673–679, 2016. McArdle disease is due to an inborn defect in the muscle isoform of glycogen phosphorylase (or “myophosphorylase”), the enzyme that catalyzes the first step of glycogenolysis. This condition is still not fully understood, and although advances in research would help patients immeasurably, these would also enhance our understanding of exercise metabolism. It has been 10 yr 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 patients with McArdle disease is still overlooked. Here, we review the role of exercise in McArdle disease with the aim to better inform health-care professionals and thus better serve the interests of patients. Recommendations for regular exercise together with preexercise 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 LIFESTYLE

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 No. 232600), show exercise intolerance as their main clinical symptom. Muscle biopsies in patients with McArdle disease 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 oxidation 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, that is, within muscle or blood (42). When the rate of demand for ATP outstrips its supply, predominantly by β-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
WHAT IS McArdle DISEASE?

McArdle disease is an autosomal recessive disorder caused by mutations in the \textit{PYGM} gene (MIM No. 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 \textit{PYGL} (liver isoform) and \textit{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) because most patients show no M-GP activity upon muscle biopsy (5,25). The prevalence of McArdle disease is thought to be largely underestimated in American (5,25) and Spanish (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. Patients with McArdle disease 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, that is, well above 200 U·L^{-1} in most patients and greater than 1,000 U·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 approximately 7 to 10 min 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 after the 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 intrafamiliar clinical heterogeneity). Acute renal failure is infrequent, for example, 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.

**FIGURE 1—**Blood lactate response to a gradual dynamic exercise test (e.g., on a cycle-ergometer) in a patient with McArdle disease versus a healthy individual. $VO_{2peak}$, peak oxygen uptake.

**DIAGNOSIS PAYING PARTICULAR ATTENTION TO CHILDREN**

Diagnosis should be made as early as possible because 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...
because it is pathognomonic for the disease. It can easily be confirmed in a 15-min cycle-ergometer test at low constant workload (e.g., 40 W) while monitoring heart rate (40).

Because 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 disease make 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. Preschool 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 hasten the genetic diagnosis because 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; 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, patients with McArdle disease usually have low aerobic power compared with their age- and sex-matched healthy peers (22), and only 3% of adult patients are able to fulfill the minimal threshold of peak oxygen uptake (VO2peak) for optimal health, that is, eight metabolic equivalents (MET) or 28 mL kg⁻¹ min⁻¹ (14).

FIGURE 2—Main clinical features of McArdle disease.
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 after a 20-yr period of inactivity (32). Older patients with McArdle disease 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 5 male patients with McArdle disease was published in 2005. Patients were trained on a cycle-ergometer at 60% to 70% of their maximal heart rate three times a week (45 min per session) for a total of 8 wk. After this training program, 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 wk. Exercise intensity was 60% to 70% of their maximal heart rate, and the duration of the sessions was increased from 30 min during the first half of the program to 40 min thereafter. Compared with baseline, patients showed higher values of peak work capacity (W), \( V\dot{O}_2\text{peak} \), and cardiac output after the training program. 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 8 months. Intensities and session duration were similar to the aforementioned studies, although patients ingested 100 g of complex carbohydrates 1 h before exercise and drank a sports drink (330 mL, equivalent to 30 g of simple carbohydrates) 5 min before exercise (see below for explanations of these nutritional recommendations). Several indicators of exercise capacity, notably ventilatory threshold and \( V\dot{O}_2\text{peak} \), improved with training.

The above studies reported that exercise interventions were beneficial and safe because no adverse effects of the training programs were observed (36). Furthermore, 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 programs, 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 approximately 40 min 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 5 min before exercise. Lastly, in 2008, Andersen and Vissing compared the effect of a carbohydrate-rich versus a protein-rich diet on patients’ exercise capacity (2). Results indicate 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 patients with McArdle disease, see (35).

Exercise seems to be the main modifier of the clinical course of McArdle disease. Over a 4-yr period, 81% of physically active patients (i.e., physical activity levels above the minimum recommendation of 150 min wk\(^{-1}\) 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 program 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 \( V\dot{O}_2\text{peak} \), 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 patients with McArdle disease 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 programs 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 Fig. 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 to stretch 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 program 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 yr). 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 approximately 60 min (the average time for recreational runners [joggers] to complete 10 km is generally 75–80 min), climbing Kilimanjaro (5895 m), completing a 32-d 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 patient with McArdle disease followed up for longest after aerobic training is a 9-yr-old boy (29). At 1 yr 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-yr adolescent (9) and in 7 middle-age adults.

![FIGURE 3—Main preexercise nutrition recommendations for patients with McArdle disease. *Not strictly needed, especially before light-moderate intensity activities or in fitter patients. Preexercise 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 overexertion.](image-url)
of both sexes (38). The adolescent undertook a 6-wk, supervised, weight lifting program of light to moderate intensity (~65%–70% of 1-repetition-maximum (IRM); two sessions per week) (9) and followed the dietary recommendations detailed in Figure 3. After training, his bench press maximal strength (9RM) and multi-power squat performance increased by approximately 27% and 6%, respectively. No myoglobinuria episodes were reported during or at the end of the program, and he was virtually asymptomatic after the training intervention (9). Santalla et al. (38) recently assessed the effects of a weight lifting training circuit program of 4-month duration and light-moderate intensity (two sessions per week) followed by a 2-month detraining period in seven adult patients with McArdle disease (five female patients), on muscle mass assessed by dual-energy x-ray absorptiometry and muscle strength, and 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 approximately 1 kg), and 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 patients with McArdle disease, 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 patients with McArdle disease need further elucidation in adequately powered randomized 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 proactive attitude of clinicians, exercise professionals, and patient associations.

The research of Alejandro Lucia, Tomà s Pinos, and Joaquin Arenas in the field of McArdle disease is funded by the Fondo de Investigaciones Sanitarias (FIS, grant numbers PI12/00914, PI13/00855, and PI14/00903) and cofinanced by FEDER. Gisela Nogales-Gadea and Alfonsina Ballester-Lopez are supported by a Miguel Servet grant (ISCIII CD14/00032, PI15/01756, and FEDER).

Authors declare no conflict of interest and that the present study does not constitute endorsement by American College of Sports Medicine.

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