Chapter

Sports and McArdle Disease (Glycogen Storage Disease Type V): Danger or Therapy?

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Abstract

McArdle disease (glycogen storage disease type V) is an inborn error of energy metabolism in the muscle. The effects of McArdle disease on physical performance have similarities with the metabolic state of marathon runners after glycogen depletion and can therefore be seen as a nature's experiment in the field of sports medicine. Many patients with McArdle disease avoid sports in general because physical activity usually leads to muscle pain and muscle cramps. Often patients therefore regard physical activity as both painful and possibly dangerous. This chapter is about the advantages and possible risks of sports for patients with McArdle disease. The scientific literature will be discussed highlighting both endurance and muscle strength exercise. It will discuss the differences of aerobic and anaerobic exercise in individuals suffering from McArdle disease. Complications as rhabdomyolysis, myoglobinuria, kidney failure, and malignant hyperthermia will be discussed. The chapter will summarize the current knowledge about the possible dangers versus possible benefits of sports for patients with McArdle disease. A summary of recommendations for physical exercise and training for McArdle patients will be provided.

Keywords: McArdle disease, glycogen storage disease type V, rhabdomyolysis, endurance exercise, muscle strength exercise, aerobic exercise, anaerobic exercise, sports medicine

1. Introduction and background

1.1 No sports?

Many people with McArdle disease do not like sports or physical activity and say therefore no to participation in sports activities or regular physical exercise. The aim of this chapter is to address patients and health care providers' queries about vMcArdle disease and sports as well as to provide guidance on physical activity for those who have to live with McArdle disease.

McArdle disease (glycogen storage disease type V) is an inborn error of energy metabolism in the muscle [1–5]. It hampers physical exercise in affected patients due to the restriction of the availability of glucose as energy source for muscular work. It can be seen as a nature's experiment in the field of sports medicine as the underlying defect of the myophosphorylase enzyme leads to metabolic effects

that are similar to the effects of glycogen depletion in marathon runners [2]. Many patients with McArdle disease (McAd) avoid sports because physical activity usually leads to muscle pain and muscle cramps. Often patients with McAd therefore regard physical activity as both painful and dangerous. On the other hand, physical activity is of great importance to manage daily life. Living is based on regular motion, and muscles have to be used in order to be healthy. Not using our muscles will in the long run lead to weakness, immobility, and frailty. Therefore people affected by McArdle disease do benefit of keeping a certain degree of fitness. Regular physical exercise might play a key role in delaying progressive muscle wasting, weakness, and frailty in later life of people affected by McAd.

- But how much physical activity is beneficial and what might be dangerous?
- Are certain types of physical exercise better than others?

These and many other questions arise when talking about physical activity and sports with patients with McAd. People with McAd do therefore need guidance on physical activity based on scientific and evidence-based facts. Due to unpleasant experience with sports in the form of pain, cramps, weakness, or myoglobinuria, many patients with McAd show a tendency to avoid sports and physical activity because they are afraid that sports may be not only painful but also harmful. Unfortunately this behavior can decrease their physical activity and physical capacity further. This chapter will shed light on McArdle disease and sports in general and try to answer the above mentioned questions.

2. Method

This chapter is based on a review of the existing publications on McArdle disease (glycogenosis type V) and sports and the authors' personal experience with the topic based on his German PhD thesis on the subject [2] and practical experience with patients with McArdle disease from sports medicine and anesthesiology. A literature search with the Medical Subject Heading (MeSH) words "McArdle disease" and "sports" was performed using the search engines PubMed and Medline. Publications that had McArdle disease and sports as a topic were included. In addition reference lists of books and other sources were assessed by hand search. An overview of the existing literature on this topic is provided.

3. McArdle disease: a nature's experiment

McArdle disease was first described in 1951 by Brian McArdle, a British neurologist. It is known by different synonyms as myophosphorylase insufficiency, glycogen storage disease type V, or myophosphorylase deficiency [1–5]. **Table 1** provides an overview of the different types of glycogen storage diseases [6]. McArdle disease is caused by a lack of myophosphorylase (alpha-1,4-glucan orthophosphate glycosyl transferase) that normally initiates muscle glycogen breakdown during exercise by removing 1,4-glycosyl groups from the glycogen molecule leading to the release of glucose-1-phosphate [1–5] and thus providing fuel for muscular work. Patients with McAd are unable to use the glycogen storage in the muscles as an energy source to enable physical activity.

In about 50% of patients with McAd, a positive family history can be found. For most of the patients, the diagnosis is first established between the age of 10 and 30 [3]. The disease is described to be autosomal recessive, although transmission

Type of glycogen storage disease	Enzyme defect	Inheritance	Organs involved	Clinical symptoms
Type 0	Glycogen synthase deficiency		Liver	Fasting hypoglycemia, tiredness, pallor, vomiting, muscle cramps
Type I **Von Gierke disease**	Glucose-6-phosphatase deficiency	Autosomal recessive	Liver, kidney	Growth retardation, hypoglycemia
Type II **Pompe disease**	Acid maltase deficiency	Autosomal recessive	Muscle, heart, liver	Hypotonia, muscle weakness (progressive), affected: proximal and respiratory muscle, cardiac enlargement and failure
Type III **Cori disease**	Debrancher enzyme deficiency	Autosomal recessive	Liver, muscle, heart	Growth retardation, muscle weakness (liver cirrhosis can occur)
Type IV **Andersen disease**	Branching enzyme deficiency	Autosomal recessive	Liver, kidney, heart, muscle	Mild hypoglycemia
Type V **McArdle disease**	Myophosphorylase deficiency	Autosomal recessive	Skeletal muscle	Exercise intolerance, muscle cramps and pain, myoglobinuria on strenuous exercise
Type VI **Hers disease**	Liver phosphorylase deficiency	Autosomal recessive	Liver	Mild hypoglycemia
Type VII **Tarui disease**	Phosphofructokinase deficiency	Autosomal recessive	Skeletal muscle	Muscle pain and fatigue on exercise. Muscle cramps and tenderness
Type VIII	Phosphorylase b kinase deficiency	X-linked recessive	Liver, brain	Ataxia, spasms, brain degeneration
Type IX	Phosphoglycerate kinase deficiency	X-linked recessive	Liver	Mild hypoglycemia
Type X	Phosphoglycerate mutase deficiency	Autosomal recessive	Liver, muscle	Exercise intolerance, muscle pain

Table 1.
Overview of glycogen storage diseases (modified from [6]).

clinically appears to be autosomal dominant in some affected families [2–4, 7]. The gene for myophosphorylase lies on chromosome 11q13. There are a number of different mutations described in the scientific literature; the most frequent mutation is named R50X [5].

The prevalence of McArdle disease is not known exactly due to the relative benign course of the disease and the often mild and frequently misinterpreted clinical symptoms. The clinical symptoms are summarized in **Table 2**. Haller has estimated the prevalence of McArdle disease in the Dallas-Fort Worth region as 1 in 100,000 [8].

As the pathophysiological effects of McAd are similar to the state of glycogen depletion in marathon runners, it is of special interest from the view of sports medicine and has been called a nature experiment [2].

- Muscle pain (myalgia)
- Fatigue
- Cramps
- Exercise intolerance
- Intermittent claudication
  - (Muscle pain on mild exertion in the calf muscle, usually attributed to peripheral artery disease)
- Second wind phenomenon
- (Exercise becomes easier after a period of moderate and tolerable exercise)
- Stiffness
- Muscle swelling after exercise
- Myoglobinuria
- Muscular atrophy
- (Mostly proximal muscles affected and in elderly patients)

Table 2.
Clinical symptoms and signs of McArdle disease [1–4].

4. Typical clinical picture and diagnosis of McArdle disease

4.1 Typical clinical picture

Typical clinical symptoms of McArdle disease are muscle pain and fatigue during exercise. Pain is often located in the knee, calf, and legs. Normally pain vanishes after a few minutes rest. Clinical symptoms and signs are shown in **Table 2** [1–4].

4.2 Diagnosis of McArdle disease

Diagnosis is based on the clinical picture, muscle biopsy, biochemical tests, exercise testing, and genetic testing [2–4, 7, 9] as listed in **Table 3**.

The absence of rising lactate is a diagnostic criterion in McAd. Usually this has been tested using the forearm ischemic exercise test [2–4]. Both Bollig [2] and Vissing and Haller [9] have suggested to use cycle ergometry testing instead of the forearm ischemic exercise test. The ischemic forearm exercise is more painful for the patients and might put them at risk for severe rhabdomyolysis and myoglobinuria. The cycle ergometry as diagnostic tool from sports medicine is useful in the diagnosis of McAd and may be used to assess the actual state of cardiopulmonary fitness and may help to give patients guidance for further training. **Figure 1** shows the results of cycle ergometry testing in a typical patient with McArdle disease [2].

- Clinical picture
- Elevated creatine kinase (CK) levels in the blood
- Absence of increased venous lactate during forearm ischemic exercise test or cycle ergometry
- Low or absent myophosphorylase activity on histochemical or biochemical examination of muscle biopsy
- Genetic testing (the muscle phosphorylase gene is located on chromosome 11q13, and several mutations have been described—the most common mutation is called R50X)

Table 3.
Diagnosis of McArdle disease [2–4, 7, 9, 10].

Workload (watt)	Heartrate / min.	Bloodpressure (mmHg)	Lactate (mmol/l)
0	76	120/85	0,8
30	116	130/-	0,8
70	164	170/-	1
110	204	180/-	0,8

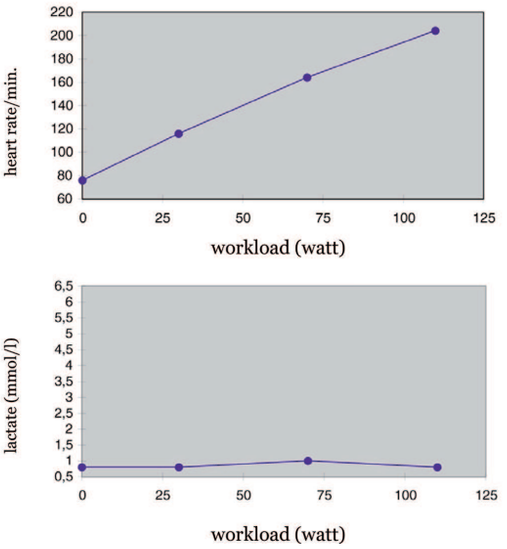

Figure 1.
Cycle ergometry of patient F.M., born 1967, 183 cm, 80 kg; modified from [2].

The prognosis of McArdle disease is usually good, and life expectancy is normal although severe cases with muscle wasting and extreme weakness and death in childhood have been described [1–4, 10].

5. Treatment options

At present there are no causal treatment options available. Some symptomatic treatment options may reduce symptoms or enhance the amount physical activity that can be tolerated. These treatment options include oral sucrose before exercise [11], a low dose of oral creatine [12], vitamin B6 [2, 10], and coenzyme Q10 [2, 10]. Our study about the use of clenbuterol over a 12-month period leads to a subjective improvement of exercise tolerance in three patients. Some relatives of the patients noted an improved exercise tolerance after clenbuterol intake over some weeks [2]. One patient from our study has used a low-dose clenbuterol (0.005–0.02 mg once daily) to enhance exercise tolerance for more than 10 years. This patient used clenbuterol for some months with regular breaks of weeks up to months between the therapy cycles. A systematic Cochrane review on pharmacological and nutritional treatment options has been published by Quinlivian et al. [12]. There do exist animal models for McArdle disease in sheep, cows, mice, and rats that may be used to test potential therapies in future studies [10]. Gene therapy of McArdle disease might be a future option, but its dangers outweigh the possible advantages at present [10].

6. Health problems and possible risks associated with McArdle disease

Patients with McArdle disease are at risk of developing myoglobinuria and even kidney failure due to rhabdomyolysis after exercise or anesthesia [2, 3, 12, 13]. Therefore, patients affected by McAd should learn how to accomplish daily activity

with McAd and how to avoid major muscle damage and the risk for massive rhabdomyolysis and acute kidney failure.

Some cases with insulin resistance and a diabetes type II-like clinical picture in patients with McArdle have been described, but there is no known connection between type I diabetes and McArdle disease [10]. Increased glycogen storage in the muscle of McArdle patients has been suggested as a probable cause of insulin resistance in McArdle patients [10]. Overweight has been observed in many patients with McAd [14]. This might be a potential risk factor for developing type II diabetes as it is for other people without McArdle disease.

Another potential problem is the possible risk of malignant hyperthermia which is a complication during general anesthesia associated with different muscular diseases. Although no case of malignant hyperthermia during anesthesia has been described in McAd so far, it is a potential risk when patients with McAd have to undergo operations with the need for general anesthesia. Therefore, precautions have to be taken by the anesthesiologist, and local or regional anesthesia may be preferred whenever feasible [6, 13].

7. Effects of physical activity and sports in patients with McArdle disease

As described above patients with McAd might suffer from exercise intolerance and pain, fatigue, and cramps during exercise, typical clinical symptoms of McArdle disease. Up to 50% of the patients with McAd show myoglobinuria, and unfortunately acute renal failure has been described in 27% following rhabdomyolysis as a result of vigorous or strenuous exercise [3]. Cases with extreme rhabdomyolysis and myoglobinuria have, e.g., been reported after a swimming competition, an asthma attack, after carrying a TV, and after the diagnostic use of the ischemic work test using a tourniquet [15–19]. The variation of creatine kinase (CK) levels in the blood has been investigated in a male with McAd over a period of several months by the author [2]. **Figure 2** shows the results from this German doctor thesis from the year 2000. The results indicated that anaerobic exercise and physical activity demanding great strength or strenuous exercise lead to huge increases in creatine kinase activity, whereas aerobic exercise did not increase blood creatine kinase levels to a great extent. Aerobic exercise was shown to be associated with lower creatine kinase levels after physical activity in a number of instances during the study period [2, 20]. This finding was later proofed by other researchers [10]. The oxygen uptake and physical ability of patients affected by McAd is usually limited to about 50% of comparable healthy individuals [2].

7.1 The second wind phenomenon

The second wind phenomenon is defined as "a period of less painful and more effective exercise associated with a decrease in heart rate after the initial period of cramping and/or weakness." [21]. Many patients with McArdle disease do experience this phenomenon that was first described by Pearson et al. [22]. During exercise this phenomenon can lead to better endurance because patients are able to exercise for a longer period and experience physical activity as less painful in the long run.

7.2 Aerobic exercise (endurance exercise)

Aerobic exercise is endurance exercise where oxygen is needed in energy production. Aerobic energy production takes some minutes to start but can help to

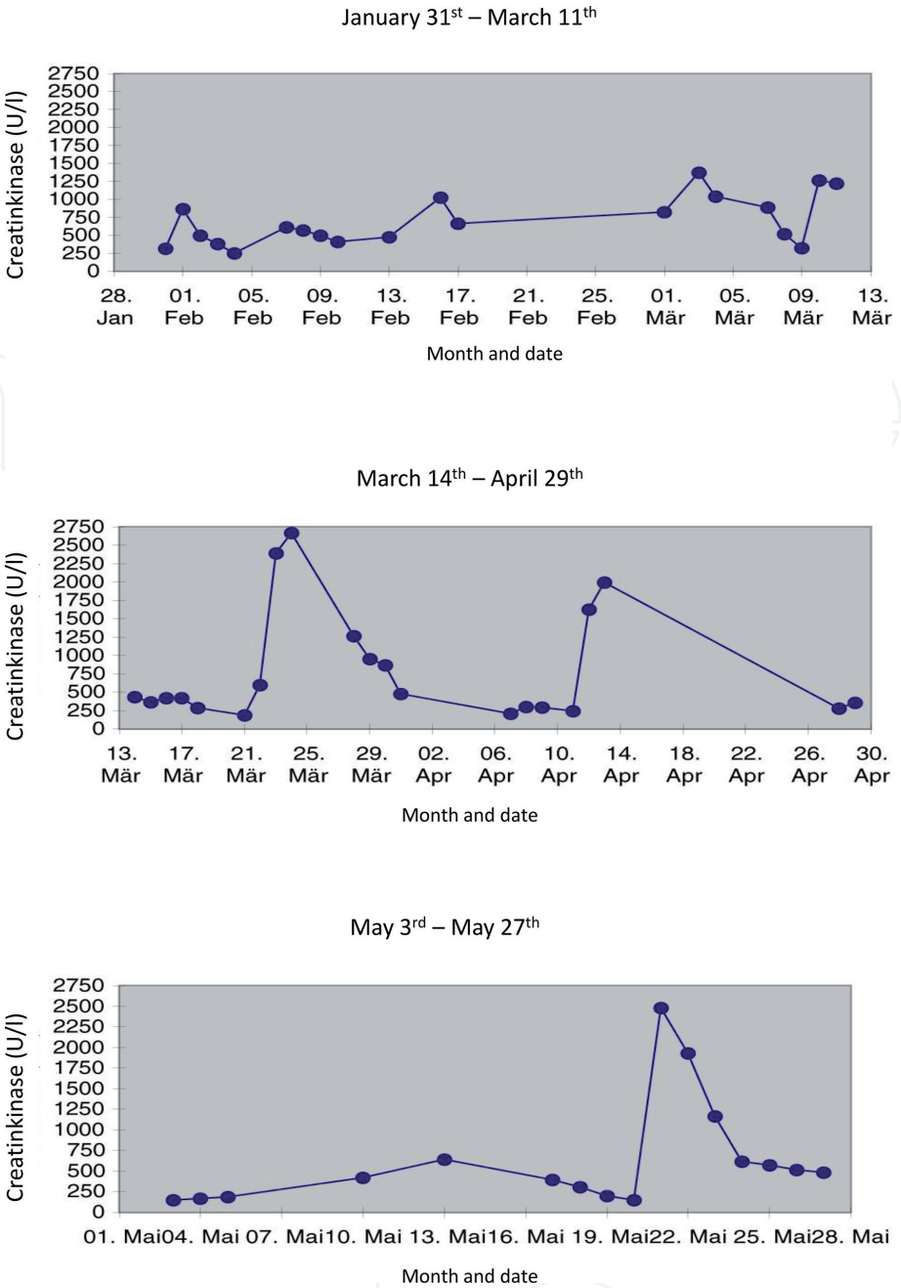

Figure 2.
Creatine kinase levels from a long-term follow-up over 5 months [modified from [2]].

supply energy for muscular activity over a longer period of time (several minutes up to several hours). Due to the lack of glucose that cannot be released from the glycogen deposits in the muscle, patients with McArdle disease rely on fatty acids, amino acids, and glucose from the liver as energy source during exercise [2, 10]. These mechanisms are based on aerobic metabolism. Patients with McAd can therefore tolerate longer periods of physical activity well if it is aerobic exercise of mild-to-moderate intensity. The work intensity that patients with McAd do tolerate can show big variations between different patients.

During the study period, different types of physical activity were recorded in a diary by the patient. Aerobic exercise as cycling and walking/hiking did not lead to CK elevation, whereas anaerobic exercise leads to CK elevation.

Different researchers have recommended aerobic training and aerobic conditioning in order to improve physical activity, oxygen uptake, cardiovascular fitness, and energy supply via the blood in McAd [2, 10, 23–26]. Especially walking and cycling with mild or moderate intensity can be recommended for all McAd

patients to improve their physical capacity [2, 10, 25–27]. Aerobic metabolism usually starts after 7–10 min of exercising. Therefore, patients with McAd should warm up with low intensity and may increase the intensity of physical work after 7–10 min. Some of the patients experience the above described second wind phenomenon.

7.3 Anaerobic exercise

During anaerobic exercise (within the first seconds and minutes or using great strength), energy is supplied by anaerobic mechanisms as anaerobic glycogenolysis without oxygen. Short periods of activity with high intensity such as running, walking upstairs, and carrying or lifting heavy weights require anaerobic metabolism. Due to the deficiency of the myophosphorylase enzyme in the muscle of McAd patients, this is hampered. Anaerobic physical activity can thus lead to muscular damage in patients with McAd and should be avoided as far as possible by patients with McAd [2, 10, 25]. Nevertheless supervised resistance training has been shown to improve muscle strength in patients with McAd [28]. Pietrusz et al. state that strength training for McArdle patients is safe when it is tailored to the patient as "short bursts of resistance activity lasting no longer than 10 seconds preceded and followed by 30 seconds to 3 minutes rest." In a case report of two McAd patients, an improvement of both muscular strength and quality of life was observed after a period with resistance training [29].

8. Discussion and conclusions

Sport is the most important therapeutical option for patients with McArdle disease. Aerobic conditioning can be recommended to all McAd patients, but anaerobic exercise may lead to muscular damage. It has been shown by different researchers that regular physical activity may lead to improved exercise capacity [2, 10, 23–26]. As we have learned from practical experience and the scientific literature, extensive physical and strenuous exercise may lead to muscle damage, myoglobinuria, and even acute kidney failure [15–19]. Nevertheless Santalla et al. and Pietrusz et al. have shown that resistance training under expert supervision is feasible and improves muscle strength in McArdle patients. But it is important that this type of training is performed under supervision in order to avoid muscle damage [28, 29]. On the other hand, a case study with a long-term follow-up of one patient with McAd has shown that mostly aerobic activity did not lead to an increase in the creatine kinase level. Instead, moderate cycling or hiking led to a decrease in the creatine kinase [2]. In the same patient, anaerobic exercise lead to increased CK levels suggesting muscle damage after carrying heavy weights [2]. In order to avoid muscle damage by vigorous exercise or in a risky way, all patients with McAd should receive sport medical advice on an individualized training plan that meets their individual training needs. In order to enhance patient compliance, common aims and routines for physical activity and sports should be established.

In conclusion, regular activity and sport are paramount for patients with McArdle disease. Patients benefit from regular physical activity. Sport should be based on aerobic conditioning such as walking and cycling, whereas anaerobic exercise of high intensity over short periods should be avoided in general. Physical activity must be individualized to the patients' capacity and needs. Some case

- Do not be afraid of physical activity.
- Individualize your personal training goals.
- Compete with yourself and not with others.
- Aerobic conditioning (walking or cycling) is the preferable training method for patients with McAd.
- Keep on doing physical activity on a regular basis three to five times a week using aerobic exercise, such as walking or cycling for about 30–40 min on each occasion.
- Regular training of mild-to-moderate intensity will improve physical capacity and may postpone weakness and muscle wasting in elderly patients.
- Preexercise nutrition may enhance physical performance.
- Resistance training should only be used under competent supervision of physicians and/or physiotherapists with experience in treating McArdle patients in order to avoid muscle damage.

Table 4.
Recommendations for physical activity for patients with McArdle disease.

reports suggest that even resistance training might be feasible, effective, and safe for patients with McAd. Obviously there is individual variation of the intensity that is appropriate for different patients. Therefore, a cooperation with a doctor experienced on sports medicine, trainer, and physiotherapist can help to establish an individualized training plan in order to maintain and possibly to improve physical capacity without increasing the danger for undesirable effects of too much physical activity.

Probably a self-monitoring of the CK blood level (like measuring blood-glucose in diabetes patients) could help to guide training and individual response to exercise in the future. More research on specially designed training programs for McAd is needed.

The following general recommendations shown in **Table 4** are based on personal experience of the author and the current state of the scientific literature [2, 10, 20–30].

As shown above, sport has therapeutic potential for people with McArdle disease. Sport is used with reason and is therefore not a danger but a powerful medicine.

Conflict of interest

The author declares no conflict of interest.

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