

## Can a Low-Carbohydrate Diet Improve Exercise Tolerance in Mcardle Disease?

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### Abstract

**Context:** McArdle disease is a rare disease of muscle metabolism caused by a deficiency of the enzyme myophosphorylase, which prevents stored muscle glycogen from being converted to glucose. The resultant effect is exercise intolerance with muscle fatigue and “cramping” within a few minutes of starting an activity, which can lead to muscle damage, rhabdomyolysis and potentially renal failure. A huge volume of literature over the last five decades suggests that a high carbohydrate diet increases insulin secretion, inhibiting the use of fat (and ketones). Since McArdle patients lack access to the majority of their stored carbohydrate, the further blockade that a high carbohydrate diet imposes has even greater implications for exercise tolerance. Nutritional Ketosis (NK) has the potential to improve exercise tolerance and ultimately reduce the risk of muscle damage and attendant complications in this patient population.

**Case report:** We report the novel experience of three patients with McArdle disease that have adopted a Low-Carbohydrate Ketogenic Diet (LCKD) to manage their exercise intolerance. In each case, a distinct improvement in activity and exercise tolerance was found. Plasma Creatine Kinase (CK) was significantly lowered in all three cases, with two patients exhibiting values within normal range. Overall, each patient described an improved quality of life.

**Conclusion:** A carbohydrate-restricted diet may provide patients with McArdle disease with a consistent energy substrate for working muscles, thereby reducing the risk of muscle damage and threat of renal failure. Further research on the use of a LCKD in McArdle disease is warranted.

**Keywords:** McArdle disease; Metabolism; Low-carbohydrate ketogenic diet; Exercise

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### Introduction

McArdle disease is a rare disorder of skeletal muscle carbohydrate metabolism, with an estimated prevalence between 1: 100,000-1:167,000 [1]. Affected individuals have mutations in both alleles of the PYGM gene, which encodes myophosphorylase, the skeletal muscle isoform of glycogen phosphorylase. McArdle disease is equally represented in both sexes and is inherited in an autosomal recessive manner [2]. A cardinal symptom of this metabolic myopathy is exercise intolerance, which is manifested by myalgia, untimely fatigue, stiffness and weakness of involved muscles, dyspnea and tachycardia upon exertion [3]. An interesting and universal objective phenomenon associated with

McArdle disease is ‘second wind’. Physiologically, ‘second wind’ represents the “lag that exists in supplying sufficient energy for working muscles as a result of deficient glycolytic muscle metabolism and the time taken for the release of glucose from the liver glycogen stores and fatty acid oxidation to provide the required energy” [4].

Although McArdle disease is not generally considered to be a life-threatening condition, serious consequences may arise due to blocked muscle glycogenolysis. Continued activity in the presence of myalgia can lead to rhabdomyolysis, and the ensuing release of myoglobin into the systemic circulation, which represents a significant threat to normal kidney function. If too

much myoglobin is released, the kidneys may become occluded leading to renal insufficiency and ultimately acute renal failure. Additionally, if there is sustained isometric muscle contraction, muscle ischemia may lead to inflammation of the fascia, potentially leading to compartment syndrome.

Noakes et al. [5] discuss how the human body can adapt to using fat as the primary fuel during submaximal exercise; thereby reducing the need for liver and muscle glycogen [5]. Even tissues thought in the past to only be able to use glucose, like the brain and muscles, can switch from glucose to ketones and fatty acids for their primary energy source [6]. The use of fatty acids and ketones as a dominant energy source is called Nutritional Ketosis (NK), and the process of metabolic change is called 'keto-adaptation' [7]. Many studies now support the use of a LCKD; typically consuming <20 g of carbohydrate per day to induce NK as a treatment for obesity and metabolic syndrome [8]. Vorgerd and Zange report on a single case study whereby a 55 year-old male with McArdle disease experienced a 3 to 10-fold improvement in exercise tolerance and a reduction in CK levels from 5300 U/l to 890 U/l while on a LCKD continuously for one year. However, there were no visible improvements in muscle energy metabolism using phosphorous magnetic resonance spectroscopy (P-MRS) [9].

Given that patients with McArdle disease are unable to obtain energy from their muscle glycogen stores, NK can provide this patient population with a consistent flow of substrates (free fatty acids & ketones) for working muscles; thereby improving exercise tolerance and ultimately reducing the risk of muscle damage and attendant complications. While many studies have explored dietary intervention in McArdle disease, at present there are no nutritional or pharmacological treatment recommendations [10]. As such, patients are left to explore alternative options (such as a LCKD) to address the insidious effects of this glycogen storage disease. To determine the potential use of a LCKD for this patient population, an online survey (n=67) of patients with McArdle disease was conducted. An overwhelming number of respondents (79%) indicated an improvement in their activities of daily living (ADL); while 76% indicated an improvement in their exercise tolerance (Reason, 2016). This paper presents a retrospective report on the novel experience of three patients with McArdle disease that have improved their exercise tolerance through adoption of a carbohydrate-restricted diet.

## Case Report

McArdle disease is considered an ultra-rare disease; and while the use of a LCKD seems promising, it has not been clinically studied amongst this patient population. Identification of retrospective cases therefore presents a distinct challenge. To increase the validity of these reports the following inclusion criteria for this retrospective case report include: DNA confirmed diagnosis (**Table 1**); adherence to a LCKD for > 6 months, pre and post LCKD CK reports, completion of subjective questionnaire, and consent (**Table 2**).

## Case 1

A 54-year old male with a lifelong history of muscle pain and fatigability that worsened upon exertion. He identified that activity/exercise was always painful and slow prior to achieving 'second wind' versus being comfortable after getting into 'second wind'. Prior to being diagnosed he consulted several doctors who suggested his muscle weakness was either due to growing pains or being lazy. Upon diagnosis, he was instructed by Dr. A. Slonim to maintain an exercise regime and a reduced carbohydrate diet. In 2014, he experimented with a nutritional fast and found that his exercise tolerance improved, which led to the discovery of a LCKD. Since 2014, he has broadly followed a LCKD. He sporadically tests his serum ketone levels and aims to achieve a level of 0.5-1.5 mmol/L. On a typical day he has a coffee with butter or whipped cream for breakfast; sardines in olive oil or chicken and green vegetables for lunch; and a protein with cauliflower or avocado with olive oil for dinner. The only beverages he consumes are water, tea, coffee and occasionally whiskey. He did not experience any side-effects upon starting a LCKD, nor has he been regularly followed by a doctor. Overall, he has more energy, no longer worries about keeping up with others, and enjoys being able to play sports without suffering muscle pain afterwards.

## Case 2

A 12-year old girl with mild symptoms of McArdle disease since the age of six. Prior to her diagnosis, she was moderately active taking ballet class, swimming lessons, skiing and playing. She consumed a classic Mediterranean diet and only drank water. When asked about her symptoms prior to being diagnosed, she indicated that she had some muscle cramps but thought all her friends did, and therefore did not tell her parents. On one occasion while learning to snowboard, she had muscle cramps so strong her teacher had to carry her down the hill. In physical education (PE) class she was assigned to the 'beginner' group (engaged in lower intensity training) as a result of her presenting exercise intolerance. At the age of nine while being treated for pneumonia, it was discovered that her plasma creatine kinase (CK) was elevated, prompting further investigation. Upon diagnosis of McArdle disease, she was instructed to limit her activity and consume a diet high in carbohydrates. After starting a high carbohydrate diet, her ADLs became increasingly more difficult, resulting in over 3 months of lost time from school within a single year. In 2014 her parents switched her to a LCKD in order to make use of her fat metabolism for energy. During this transition she experienced transient weakness, headaches and nausea. Initially, her ketone levels were checked several times per day by blood, and at present are being checked every other day by breath. On average her ketone level is 6 mmol/L. An example of a typical day's food intake includes an omelette with butter and cheese for breakfast; chicken with butter and a green salad with oil for lunch; and beef tenderloin with cream, spinach and butter for dinner. Salami slices are regularly consumed for snacks and water is the only beverage consumed. She is regularly followed by a healthcare team at *Karolinska Institute, Stockholm*. Her parents have indicated that a LCKD has resulted in a return to normal life.

**Table 1** Demographic data.

Case	Gender	Current Age	Age McArdle's symptoms first presented	Age at Diagnosis	PYGM Mutations
1	M	54	3	43	p.R50X; p.R50X
2	F	12	6	9	p.R50X; p.Leu397Pro
3	F	45	10	38	p.R50X; p.Thr672Ile

**Table 2** Clinical response: Not in ketosis and while in ketosis.

Case	Not in Ketosis		In Ketosis	
	CK	Exercise Tolerance	CK	Exercise Tolerance
1	1648 U/L	From childhood, would have to stop due to muscle pain, especially early in any activity or if there was an incline. Walking or cycling uphill was always a challenge, with pain starting in the legs and progressing to the upper body until there would be no alternative but to stop and rest. After resting, could then carry on slowly. As a result of exercise intolerance, walking, running or cycling with friends was avoided. At school, would try anything to get out of having to run or participate in cross-country events.		Exercise intolerance is distinctly less. Can start walking at a faster pace in ketosis. Am able to jog and exercise on a completely different level. Before LCKD, lifetime personal best for a 50-minute treadmill session was average speed of 4.5 mph, that is now a bad day. On LCKD, new personal best is an average speed 5.5 mph. Limits are now more down to basic fitness level, rather than due to McArdles. There is no question a LCKD has improved both aerobic and anaerobic activity tolerance.
2	22,271 U/L	Upon diagnosis, was advised to begin a high carbohydrate diet. Within a few months, exercise intolerance worsened. Was only able to walk for 20 minutes @ 0.75-1.1 mph. Could climb approximately 20 steps. Began to have problems in daily activities, like walking, eating, bathing and playing. After a few months needed to use a wheelchair four days/week due to muscle damage of the leg muscles.	494 U/L	Exercise tolerance dramatically improved once in ketosis. However due to prolonged inactivity while on a high carbohydrate diet, it has taken a few months to regain aerobic fitness. Personal care, playing with other kids, attendance at school have been dramatically improved on a LCKD. Use of a wheelchair is no longer required, therefore PE classes have been restarted. Aerobic function has improved to the level of being able to walk 3.1 mph for 3 miles.
3	10,744 U/L	Experienced muscle failure, muscle spasm and flu-like symptoms regularly. With age, muscle pain was more prevalent. ADLs would cause fatigue and muscle cramps. Exercise seemed to get harder and harder to maintain with age.	150 U/L*	Overall CK is much lower while on a LCKD. No longer experience flu-like symptoms. Aerobically, can run on the treadmill from the start at about 5.5-6.0 mph for 2-3 minutes at a time, and then slower for prolonged periods. There is no need to wait until 'second wind'. Anaerobically, weight training is easier, no longer suffering from muscle aches and pain afterwards.

Reference Range: Males >18 years: 52-336 U/L; Females 8-14 years: 91-391 U/L & >18 years: 38-176 U/L; \*within normal reference range

### Case 3

A 45-year old female with a history of muscle failure and muscle spasms since the age of ten. While she noticed an improved activity tolerance and decreased heart rate (HR) once in 'second wind', she indicated that it seemed hard for her to get there and didn't notice a big difference. In 2013 she set out to lose weight using the Atkins diet. While on the diet she noticed that she felt as though she had more energy. To test her theory, she purposely went out of ketosis and engaged in exercise. Twenty-four hours later, she sought medical treatment for flu-like symptoms; her CK was 12,000 U/L. Several months later, in ketosis, she had performed the same workout. Twenty-four hours thereafter she felt fine; her CK was 3000 U/L. She periodically checks her ketone levels with urine strips and aims to be in the range of 1.5-4 mmol/L. A typical day's intake consists of a quarter cup of full fat yogurt for breakfast; salad with protein and fatty dressing for lunch; and meat with a fat, green vegetable, and egg with mayonnaise for dinner. Water is the only beverage consumed

and macadamia nuts and avocado are her preferred snacks. She is being monitored regularly by her primary care practitioner. She states that she really doesn't suffer any longer, other than if she engages in prolonged anaerobic activities - such as heavy lifting.

With each case, a distinct improvement in activity and exercise tolerance was reported. To highlight functional improvement, both objective (plasma CK) and subjective data are presented. Of note, the average plasma CK for people with McArdles is >2000 U/L [11]; yet CK was found to be within the normal range for Case 1 and 3 while in NK, with Case 2 being only slightly elevated. These findings support the proposition that patients with McArdle disease may benefit from a nutritional management strategy that enables the body to become keto-adapted.

### Discussion

It is possible that the consumption of dietary carbohydrate is exacerbating exercise intolerance in people with McArdle disease. In this paper we describe the improvement in activity

and exercise tolerance for three patients with McArdle disease while consuming a LCKD. In 1963 the Randle Cycle (aka 'the glucose-fatty acid cycle') was proposed [12]. The contention was that fuel selection during human activity, from ADL to performance in elite sport, has been ultimately predicated on environmental availability, and that availability was a key factor in the evolution of human metabolism, being conditioned as it was, by substrate availability and use. Accordingly, the authors make it very clear that the glucose-fatty acid cycle is not a metabolic cycle but rather a cycle of 'food partitioning'. Humans evolved as hunter gatherers and so feast and famine was the 'norm'. Animal protein and fat were often eaten for a number of days following a kill, subsequent to 1-3 days of fasting when hunts were unsuccessful; most of the time dietary carbohydrate was scarce. In autumn, the diet would have been supplemented with berries, nuts and seeds. So, the imperative was the requirement to store fuel substrate for times when fasting was obligatory (i.e. after failed hunts). Food sources from the environment were predominantly sources of fat and protein and so when larger amounts of carbohydrates were consumed, it was a signal of the need to store more fuel substrate.

Carbohydrates stimulate insulin secretion, which in turn facilitates the acute use of carbohydrates as a fuel substrate, but it also drives fat storage and inhibits fat catabolism. The predominant storage of fat is logical since fat is more caloric dense, yielding 37 kJ of energy per gram vs. 16 kJ per gram available from carbohydrate. For example, a healthy 70 kg man who has 15% body fat has just over 500 g of stored carbohydrate; an energy store of 8500 kJ, but around 10 kg of stored fat representing 370000 kJ.

Compared with the general population, individuals with McArdle disease have a similar amount of carbohydrate in the liver (100 g), the same small amount (3 g) in the systemic circulation, but have a supra-physiological/pathological storage of glycogen in skeletal muscle. An inability to access 80% of stored carbohydrate makes it very difficult to meet the demand for adenosine triphosphate (ATP), both at the beginning of physical activity and where sustained activity requires even very low absolute exercise intensity.

An alternative means is therefore required to provide ATP at a greater rate to minimize myalgia and reduce the risks of muscle damage; particularly prior to 'second wind'. Exogenous administration of glucose (sports drink for example) may be a solution for the risks of imminent muscle damage but will inhibit

fat oxidation in the short, medium and long term. So, this is really not an ideal solution except *in extremis*. Since humans possess vast stores of fat, relative to the more finite carbohydrate stores, it logically makes sense to minimize the insulin response that results from ingestion of foods with a high glycemic index. Doing so, will reduce or remove the block on fat metabolism, and by limiting dietary intake of carbohydrate, also potentiate the provision of ketone bodies, a fuel which the brain preferentially uses over glucose.

Ketones are as desirable a substrate to muscle as glucose, and since they do not require, energetic transport across the mitochondrial membrane, and 'leap-frog'  $\beta$ -oxidation, provide ATP much more quickly than from fat catabolism. Ketone bodies also appear to exert a preventative impact on muscle protein breakdown. Specifically, studies have shown that the ketone bodies can significantly spare muscle loss, whilst also having the ability to promote protein synthesis in both trained [13] and untrained individuals [14]. Previous studies in fat metabolism amongst patients with McArdle disease demonstrate an improvement in ventilatory response, exercise capacity, and cardiac output relative to oxygen uptake [15]. While further study is required, it would seem that adoption of a LCKD for patients with McArdle disease may improve activity and exercise tolerance. Once keto-adapted, patients are more likely to be able to engage in exercise much less haltingly, may not need to *wait* for 'second wind' (i.e. any change in substrate use), and may be able to sustain exercise at a higher rate for longer periods of time. This would allow for a far higher function, making the locomotive tasks associated with ADLs much more manageable in the short term. In the long term however, it means that patients could achieve almost the same level of health benefit from physical activity as those across the general population; thereby minimizing the risk of secondary conditions (coronary heart disease, hypertension, obesity, atheroma, stroke, cancer, etc.) which are, now well-documented consequences of physical inactivity.

In conclusion, a LCKD has been found to have a positive effect on activity and exercise tolerance for three patients with McArdle disease. Beyond a noticeable improvement in functional ability, these patients also reported an improved overall quality of life. In all probability, this novel dietary strategy could provide patients with McArdle disease with a consistent energy substrate for working muscles, thereby reducing the risk of muscle damage and the threat of renal failure that is particularly prominent prior to second wind. Further research on the use of a LCKD in McArdle disease is warranted.

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