Understanding McArdle Disease

Overview

- What is McArdle disease?
- Understanding Muscle Metabolism
  - What should happen
  - What happens in McArdle disease
- Importance of 'Second Wind'
- Typical Symptoms
- Impact on day-to-day life
- Management Strategies
- Access to Care

McArdle disease is…

Categorized as a	METABOLIC [chemical reactions] MYOPATHY [disease of the muscle]
Also known as	McArdle's, McArdle syndrome, Muscle Phosphorylase Deficiency, Myophosphorylase Deficiency, Muscle Glycogen Phosphorylase Deficiency, Glycogen Storage Disease Type 5
Named after	Dr. Brian McArdle a British neurologist who first published a paper describing a patient with the disease in 1951.

McArdle disease…

Is an **ultra rare** disease of muscle metabolism

-> estimated prevalence is 1:100,000

Is **inherited** in an autosomal recessive manner

-> we get one mutated gene from each parent

Occurs due to **mutations** in the PYGM gene

-> prevent the production of the enzyme myophosphorylase

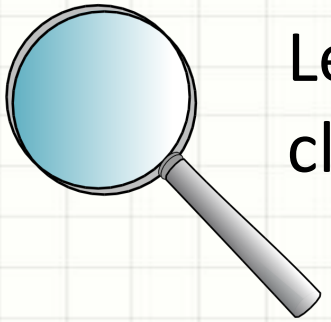
-> cannot convert muscle glycogen into glucose

Results in a lack of **fuel** [muscle glycogen] for working muscles

-> reduced fuel [glucose] during physical activity [activities of daily living - ADL] and exercise

-> may lead to muscle breakdown - rhabdomyolysis, myoglobinuria, acute renal failure, compartment syndrome

Muscle Metabolism



Let's take a
closer look at …

- How energy is transported to our muscles
- What SHOULD happen AND what ACTUALLY happens in McArdle disease

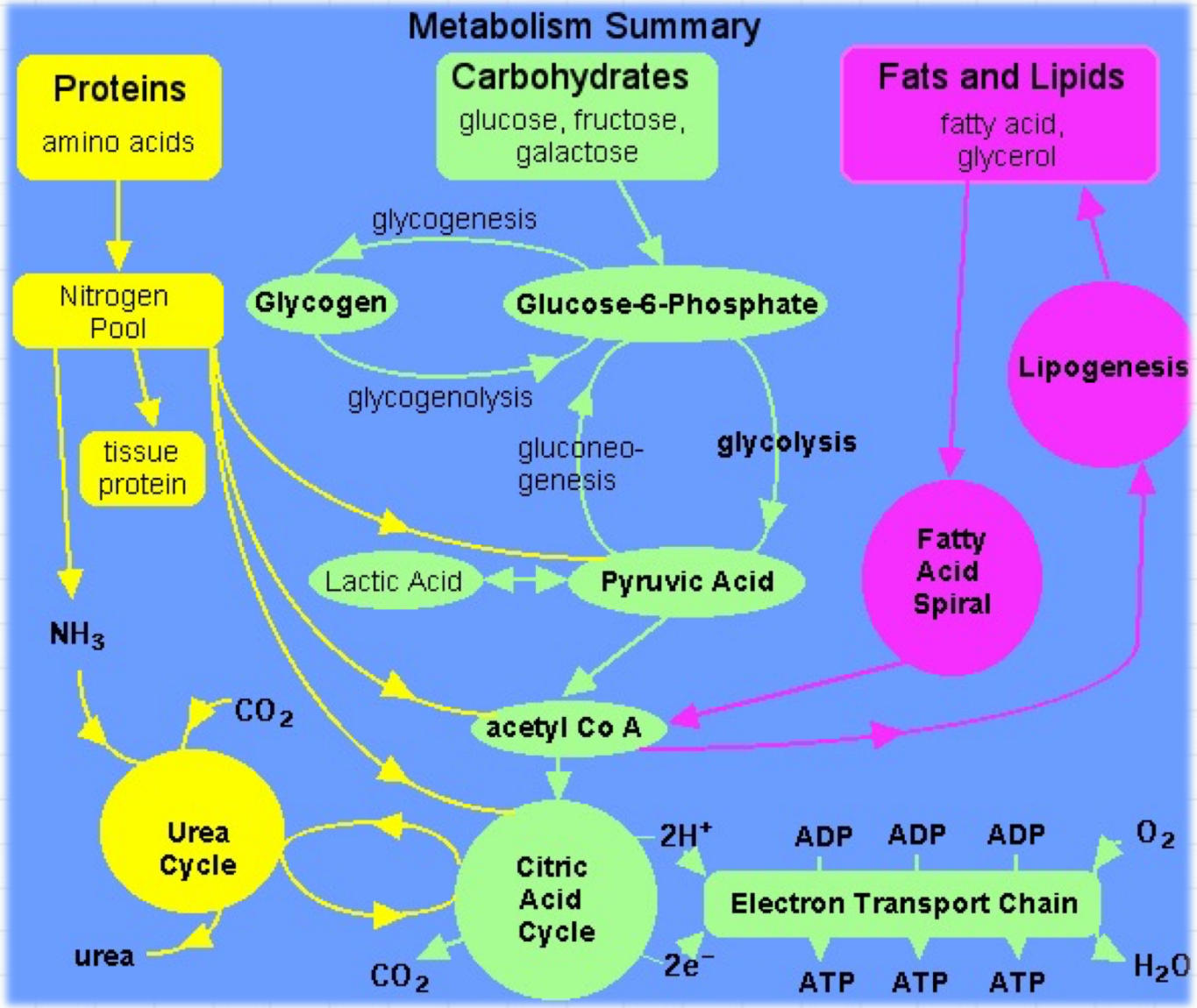
Muscle Metabolism

- THE ENERGY the body uses comes originally from the FOOD 🍎🥑🥩 we eat to produce ADENOSINE TRI-PHOSPHATE (ATP) - the body's currency for energy
- Muscle cells use ATP to contract and relax

*More about energy and ATP in Nutrition Presentation

Muscle Metabolism

FOOD
turns into
ENERGY
ATP



Muscle Metabolism

Throughout the day, the body seamlessly switches between two types of metabolism to provide the ENERGY required to carry out all activities

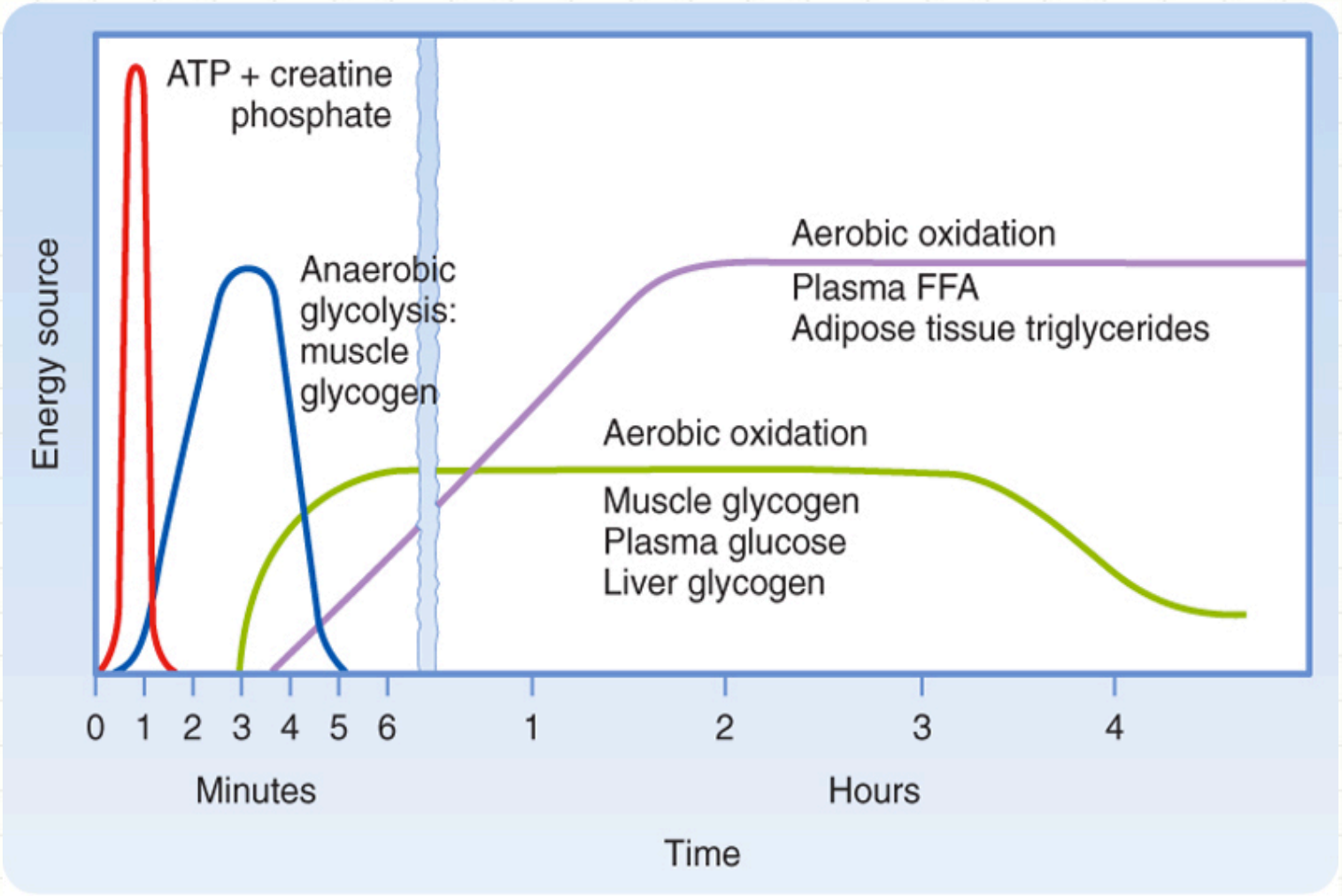
Aerobic Metabolism

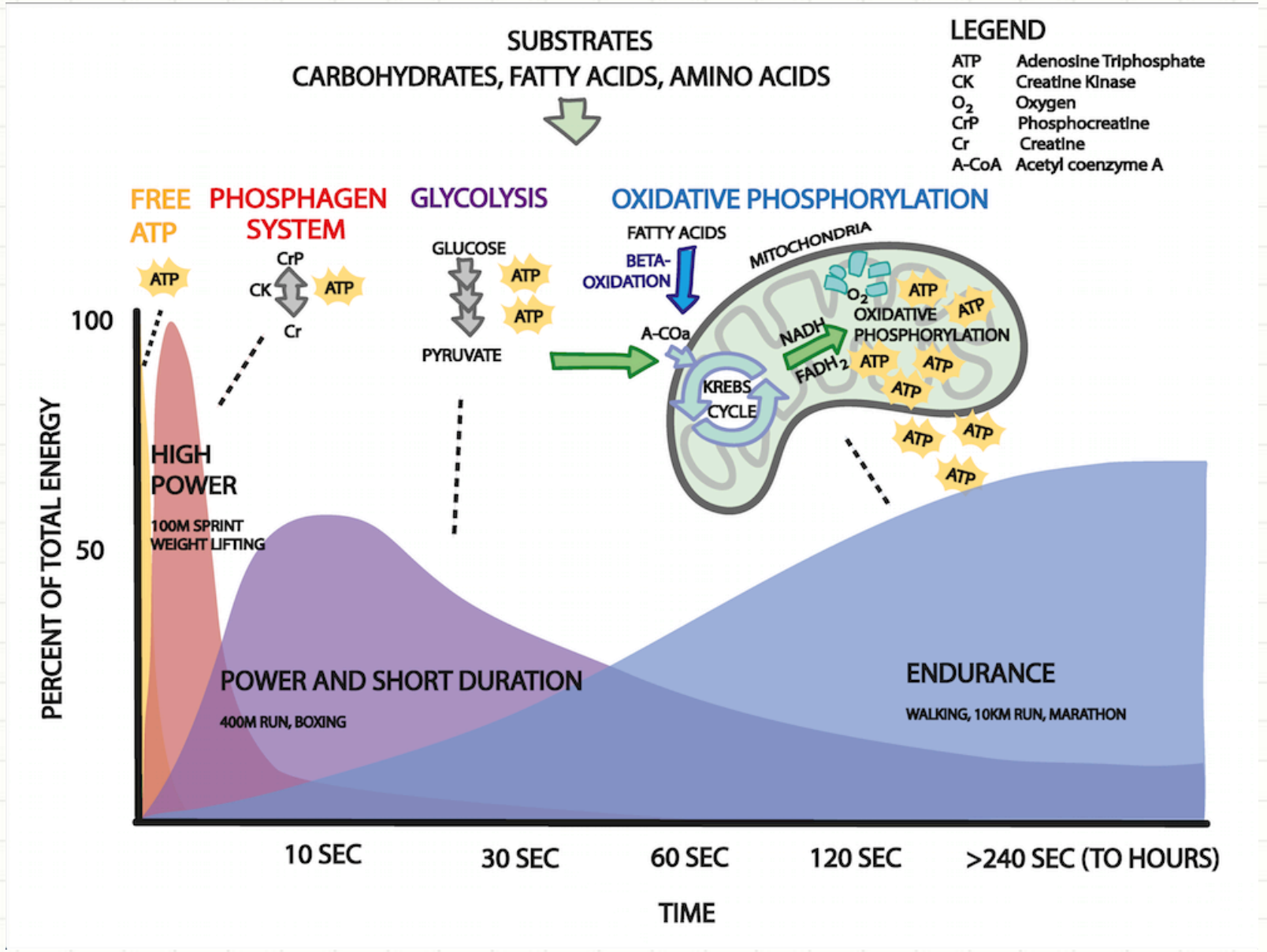
- Creation of energy through the combustion of carbohydrates, amino acids, and fats in the presence of oxygen
- Used for sustained production of energy – walking, jogging, swimming, etc.

Anaerobic Metabolism

- Creation of energy through the combustion of carbohydrates in the absence of oxygen
- Used for short bursts of intense activity - sprinting, weight-lifting, etc.

Muscle Metabolism



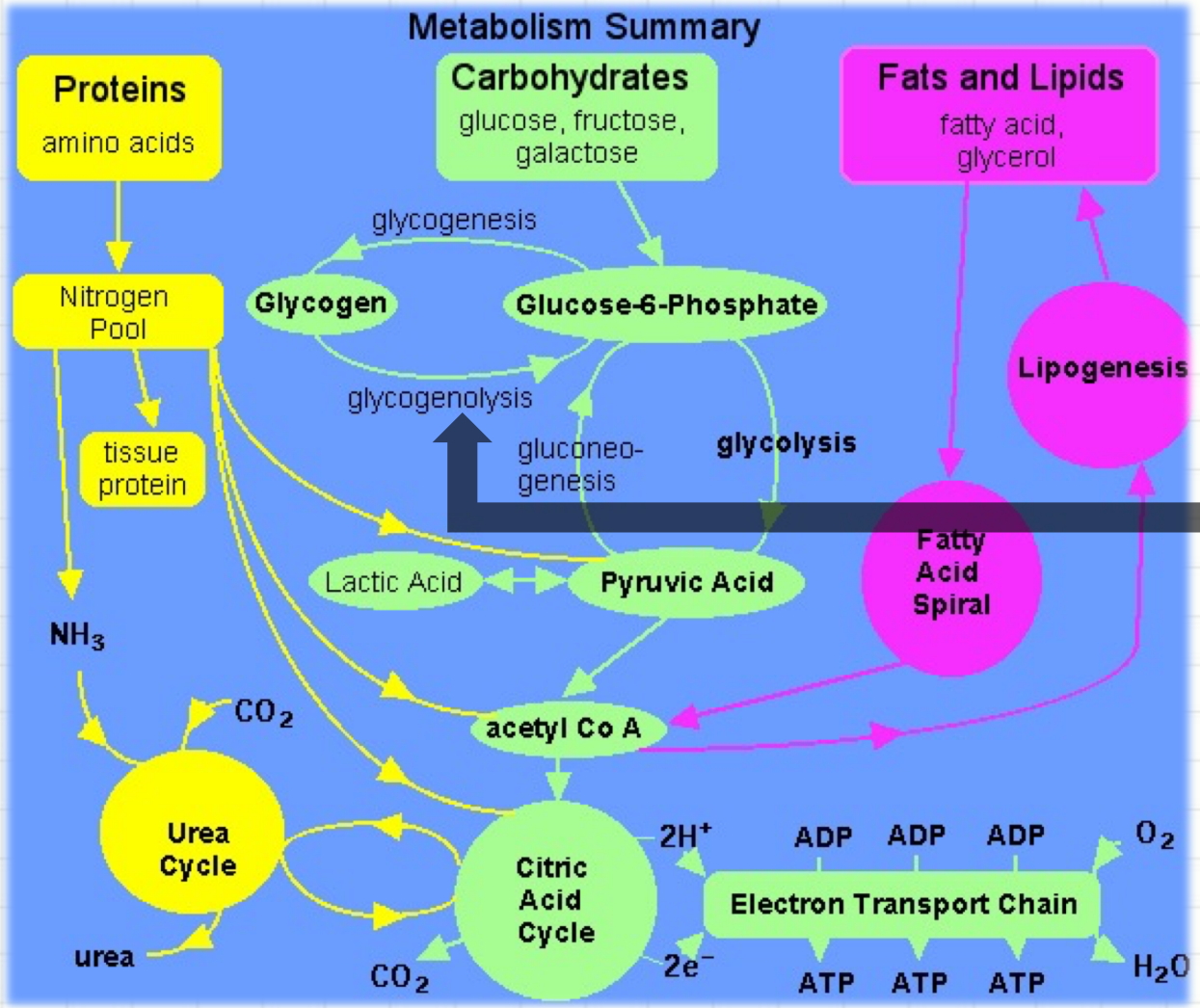


https://fitnessgenes.com/blog/energy-systems-used-during-exercise/

Muscle Metabolism

- Protein metabolism is functioning (aerobic)
- Fat metabolism is functioning (aerobic)
- Carbohydrate metabolism is impaired
  - Liver Glycogen (aerobic)
  - Blood Glucose (aerobic)
  - Muscle Glycogen (80% of stored CHO) (anaerobic)

Muscle Metabolism

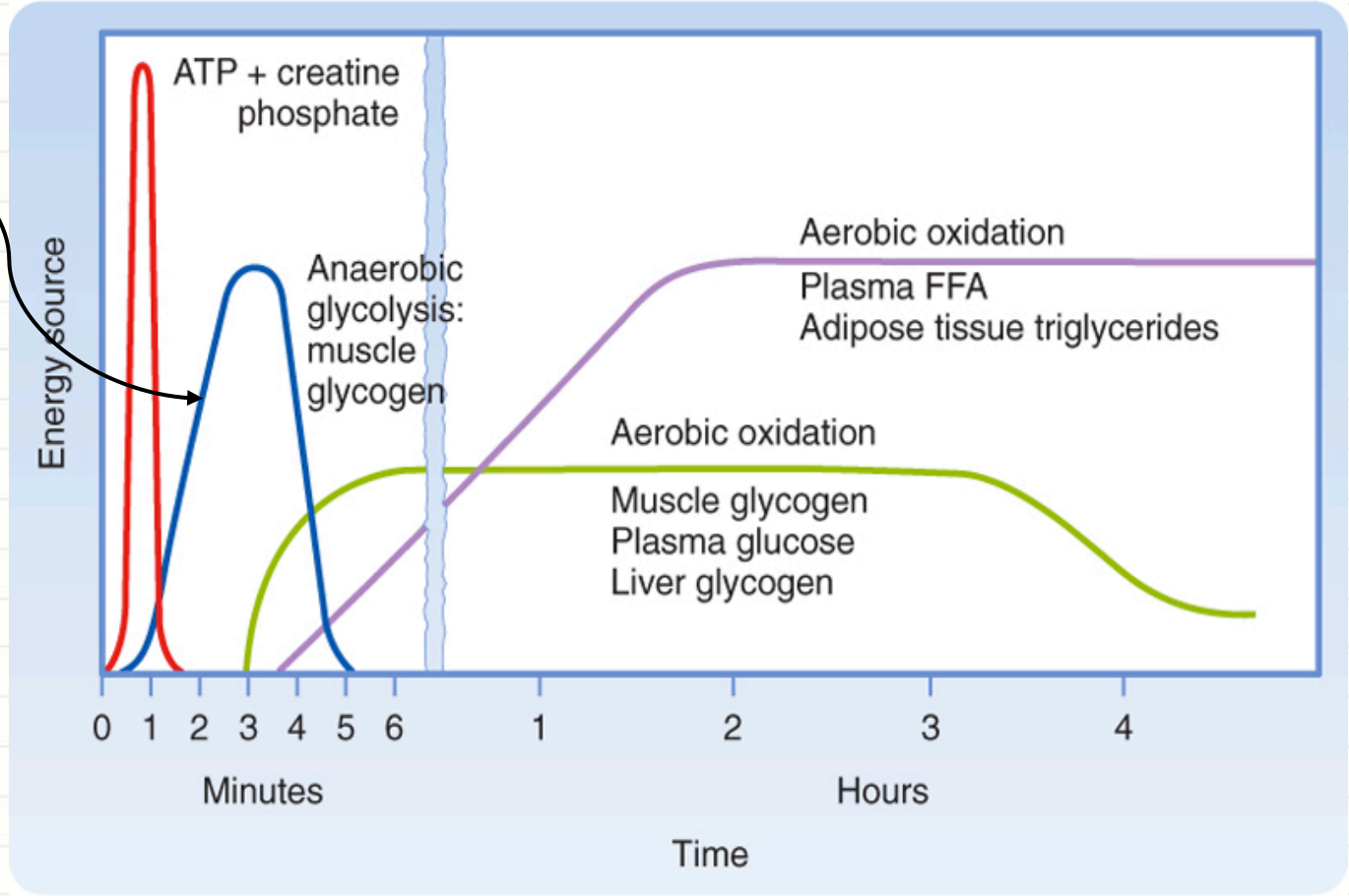


Missing enzyme prevents breakdown of

MUSCLE GLYCOGEN

Muscle Metabolism

Blocked in McArdle Disease



Muscle Metabolism

Aerobic Metabolism

Anaerobic Metabolism

Muscle Metabolism

Because individuals with McArdle disease rely on aerobic metabolism to fuel their muscles, it is important to improve aerobic capacity

AEROBIC ⟷ AEROBIC/ANAEROBIC TRANSITION ⟷ ANAEROBIC

Aerobic endurance increases when our muscles can uptake more O2 (higher anaerobic threshold) allowing us to do more activity/exercise without pain/cramping

- Muscular changes – fibre size, blood and oxygen supply and efficiency of functioning
- Improved energy production

Importance of Second Wind

An interesting and universal objective phenomenon associated with McArdle disease is '*SECOND WIND*'; which is characterized by 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

'SECOND WIND' generally begins approximately 8 minutes after the onset of moderate activity despite no change in work rate. 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

(Scalo et al., 2014, p. 5[illegible]).

Typical Symptoms

Physical

Psychosocial

Symptoms

Physical

- Cardinal symptom is exercise/activity intolerance*
- Untimely fatigue
- Stiffness & weakness of involved muscles
- Myalgia (muscle pain)
- Dyspnea (shortness of breathe)
- Tachycardia (elevated heart rate)

} upon exertion

→ Adverse Events (rhabdomyolysis, myoglobinuria, acute renal failure, compartment syndrome)

EXERCISE vs PHYSICAL ACTIVITY

… what is the difference and why is it important?

PHYSICAL ACTIVITY (PA) is defined as any bodily movement produced by skeletal muscles that result in energy expenditure.

EXERCISE, is a subcategory of PA and is defined as activity that is planned, structured, repetitive and purposive in the sense that improvement or maintenance of one or more component of physical fitness is the objective.

Ceria-Ulep et al, 2011

Given the ‘planned’ nature of exercise, one may argue that ‘formal exercise’ is easier for patients with GSDV to manage over PA. With ‘exercise’, patients can utilize well-documented strategies, such as the intake of 37g of sucrose 5 minutes pre-exercise, and carefully transitioning into ‘second wind’.

Unfortunately, these strategies are difficult to implement during activities of daily living (ADLs) given that the majority of ADLs occur in a time frame shorter than required to get into ‘second wind’ (<8min).

It is important to differentiate between EXERCISE and PA, as the two concepts often have different meanings amongst patients, clinicians, and researchers. For individuals with GSDV, the importance of making this distinction is crucial in order to ensure proper guidance is provided and the nuanced difference between the two is understood

Symptoms

Psychosocial

- Anecdotal reports of childhood trauma include, everyday embarrassment, depression and fear, and the role that a delayed diagnosis may contribute to these experiences

- A 2016 survey (N=290) found that patients with McArdle disease felt frustrated, embarrassed and that others did not understand how they were feeling

Birch, 2011, Reason, 2016

Symptoms

Table 8: 2016 Survey

How Often During the Past Four Weeks…(N = 290)

How often…	None of the time to some of the time	A good bit of time to all of the time
Were you frustrated about McArdle disease	114 (**39.3%**)	173 (**59.7%**)
Were you embarrassed about having to stop and rest because of McArdle disease	117 (**40.3%**)	171 (**58.7%**)
Did you feel others did not understand how you are feeling	101 (**34.8%**)	189 (**65.2%**)

Numbers in parentheses indicate percentages by row

Impact on Day-to-Day Life

- Living with the unknown (late diagnosis, mis-diagnosis, no diagnosis)
- Lack of information & awareness (patients, families, clinicians)
- Maintaining positive energy balance (not emptying the reservoir)
- Differentiate ‘okay’ pain with ‘not-okay pain’
- Comorbidities (relationship between McArdles and - - -)
- Access to Care (finding a physician that has a good understanding)
- Activities of Daily Living (ADLs)
  - Managing McArdles at work/school/home
- Quality of Life (QoL)
- Psychosocial impact (withdraw from activities, peer pressure, anxiety, depression)

Andrew will discuss further

Management Strategies

- Access to accurate diagnostic methods (timely diagnosis)
- Regular assessments (blood work, aerobic fitness, confirmation of second wind)
- Information and guidance
  - Second Wind
  - Caution with anaerobic activity
  - Regular physical activity
  - Nutrition
  - Awareness of warning signs re: adverse events
- Multidisciplinary support (dietician, psychologist, physiotherapist)
- Ongoing communication between primary and specialist care

Access and Care Survey 2019

Access and Care

Access and Care	%
Assessments (n = 257)	
Exercise assessment	24%
Routine blood work	67%
Nutritional assessment	22%
Option to meet with psychologist	11%
Option to meet with physiotherapist	11%
Information received (n=257)	
Importance of regular aerobic exercise	50%
Second wind	26%
Importance of avoiding anaerobic activity	43%
Ingestion of 37 grams of sucrose	28%
No information	36%
Frequency of ED visits in past 12 months (n = 258)	
Not at all	70%
1-3 times	25%
> 4 times	5%
Admitted to hospital past 12 months (n=258)	
No	75%
Yes	25%

Access to Care

Aug 2019 Survey n=256

👉 50% NEVER see a McArdle disease specialist

👉 22% less than once/year

👉 19% once/year

👉 7% every 6 months

TO ADDRESS THESE CHALLENGES:

- European Union Committee of Experts on Rare Diseases (EUCERD) recommends the use of a Centre of Expertise (CoE) to provide comprehensive diagnostic and disease management services
- Reference Networks (RN) may provide an alternate model for clinicians and CoEs to share knowledge and expertise
- Clinical Practice Guidelines (CPGs)

Without access to informed clinical support, patients do not learn the appropriate day-to-day management skills and continue to regard PHYSICAL ACTIVITY as a trigger for symptom occurrence, rather than a safe and effective treatment option. This in turn further impairs the clinical course of the disease, impacting both ADLs and QoL.

IAMGSD

International Association for
Muscle Glycogen Storage Disease

Our objectives

- **RAISE** awareness amongst the medical profession, schools, sports clubs, and other relevant groups.
- Provide **SUPPORT** for patients, organizations and medical professionals.
- **ADVOCATE** the patient viewpoint and needs to government, patient organizations and medical professionals.
- **DISSEMINATE** standards and best practice.
- **CONTRIBUTE** to the planning of research projects and to support and assist those projects.
- **FACILITATE** communications between organizations, especially internationally.
- Work to **REDUCE** the average age of diagnosis to age 10 or less.