McArdle's disease: alterations in the activity of glycogen phosphorylase in the muscle.

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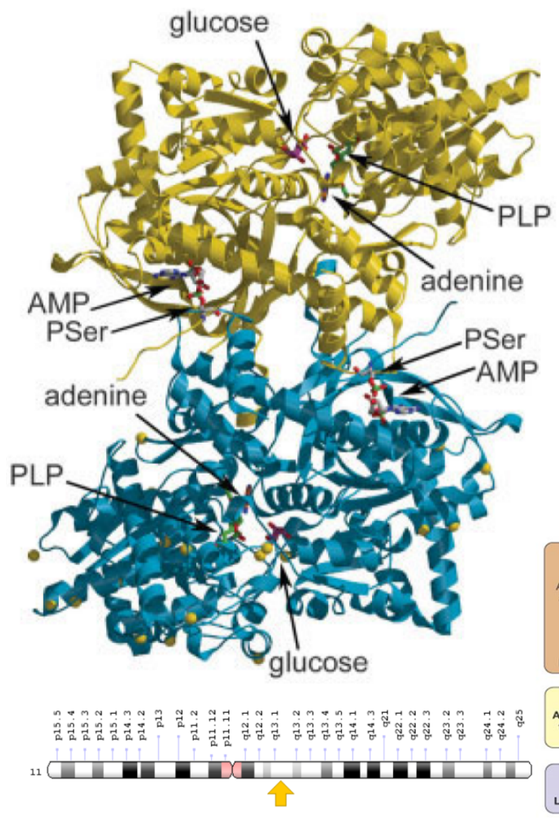
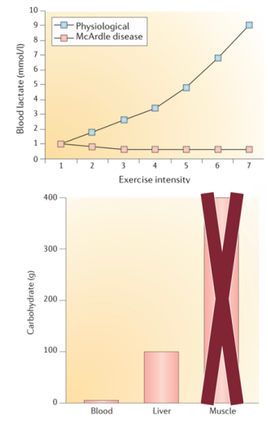
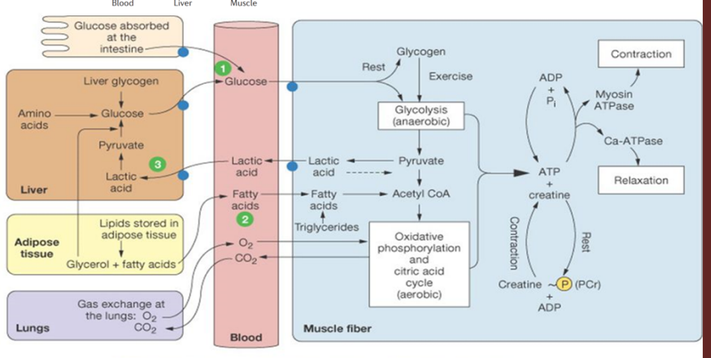
Abstract

Skeletal muscle disorders of glycogenolysis and glycolysis account for most of the conditions collectively named glycogen storage diseases (GSDs). These disorders are rare and are caused by autosomal or X-linked recessive mutations that result in a specific enzyme deficiency. The object of my study is McArdle's disease (GSD V), the most common of these disorders with an estimated prevalence of 1:100,000-1:167,000; it is caused by mutations in the gene encoding muscle glycogen phosphorylase (PYGM), which catalyzes the first step of muscle glycogen breakdown, leading to the inability to utilize muscle glycogen as an energy substrate.
The disease usually causes exercise intolerance, in the form of acute ‘‘crises’’ of early fatigue, myalgia, and contractures that can be accompanied by rhabdomyolysis and myoglobinuria. Patients range from slightly to severely affected, including in some cases, limitations in daily activities. The misdiagnosis is not uncommon because several other conditions such as muscular dystrophy and muscle channelopathies can manifest with similar symptoms.
It is shown how a simple exercise test performed in the clinic, can however help to identify patients by revealing the second wind phenomenon which is pathognomonic of the condition.
The disease present almost ~150 mutations described in the PYGM gene, the most common mutation p.R50X and the phenotype-genotype correlation is not identifiable.
Is shown in detail the metabolic alterations induced by the inability to promote glycogen at muscle level and what happens during anaerobic exercise.
Lastly, it is reported the role of fat metabolism in McArdle’s disease through the manipulating of free fatty acid availability for oxidation during exercise.







12 Minute walk test.

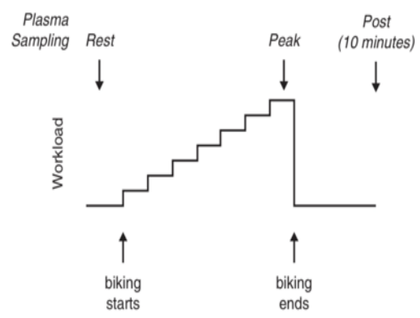
Simple testing for the diagnosis of the pathology.
The “second wind” represents the delay that exists in providing sufficient energy for the release of glucose from the glycogen stores by the liver and the oxidation of fatty acids.

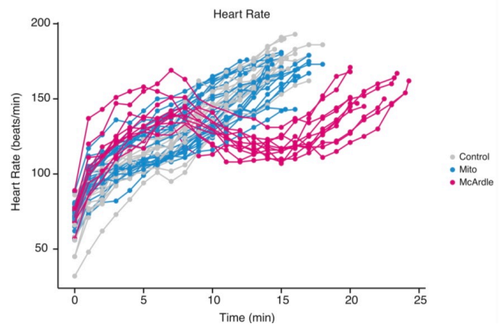
Time	Walking speed	Distance covered (m)	Heart rate	Borg Pain Rating
1	-	55	90	0
2	-	120	95	1
3	Slowed down	180	100	2
4	-	240	109	3
5	Slowed down	290	108	3
6	-	344	113	2.5
7	-	404	116	2
8	-	460	111	1.5
9	-	530	111	1.5
10	-	590	106	1
11	-	664	107	0.5
12	-	730	104	0

The “second wind” phenomenon manifests in all McArdle patients.

Demographic	*n* Unique	Age, y	% Male	Height, cm	Weight, kg	BMI, kg/m^2	Venous lactate at rest, mM	Creatine kinase at rest, U/L
Controls	12	34 ± 10	33	169 ± 10	68 ± 11	24 ± 3	0.93 ± 0.26	115 ± 12
Mito patients	21	44 ± 9	29	166 ± 7	68 ± 14	25 ± 4	1.45 ± 0.59	191 ± 21
McArdle patients	12	35 ± 19	58	173 ± 9	76 ± 17	25 ± 5	0.75 ± 0.23	7,027 ± 13,679

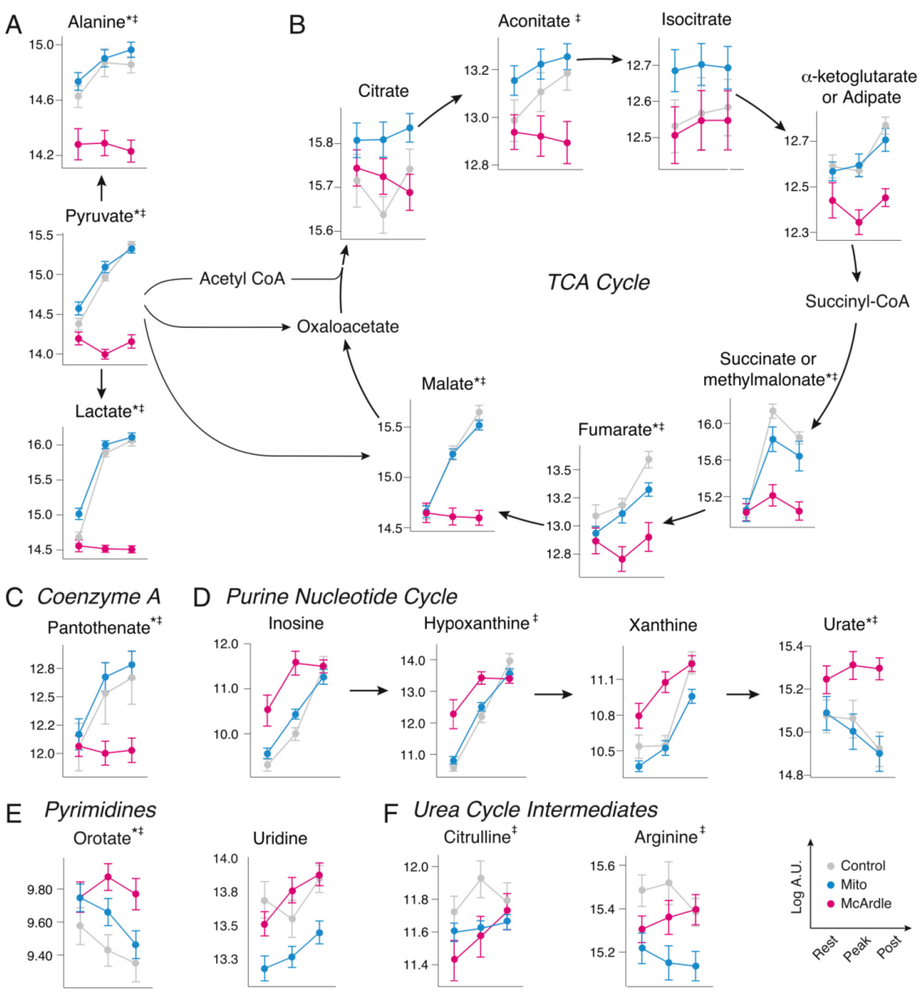
Values are expressed as mean ± SD.





Metabolic alterations in Mcardle's disease.

The levels of metabolites at rest and during exercise follow excursions which are significantly different in McArdle patients compared to the control.



The free fatty acids (FFAs) could help in McArdle's disease ?

Impaired cycle flow of (TCA) is a central mechanism of limited oxidative capacity in this disorder.