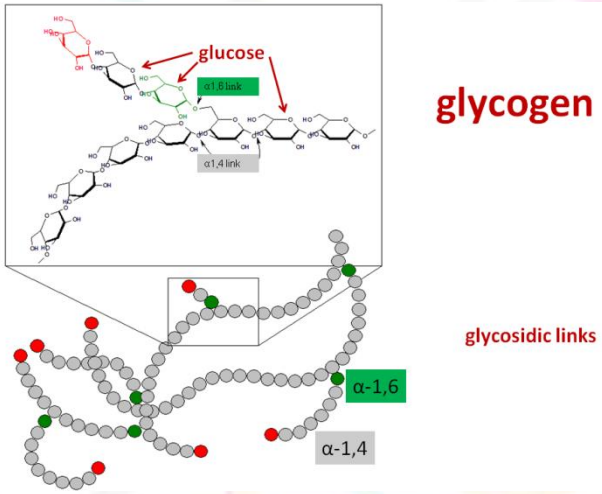
# MUSCULAR GLYCOGENOSIS

## WHAT ARE GLYCOGENOSIS?

The glycogenosis or glycogen storage diseases (GSD) are a group of inherited disorders that affect glycogen metabolism, either its degradation to glucose or its synthesis, which can be scarce or abnormal.

## WHAT IS GLYCOGEN?

Glycogen is a **polymer** consisting of **highly branched glucose chains.** These chains are composed by α-1,4 glycosidic bonds (amylose: 90% of them) which are branched by α-1,6 glycosidic bonds (amylopectin: the remaining 10%). This structure provides high solubility and many access points to the glycogenolytic enzymes, which can hydrolyze (break) glycogen easily when appropriate.

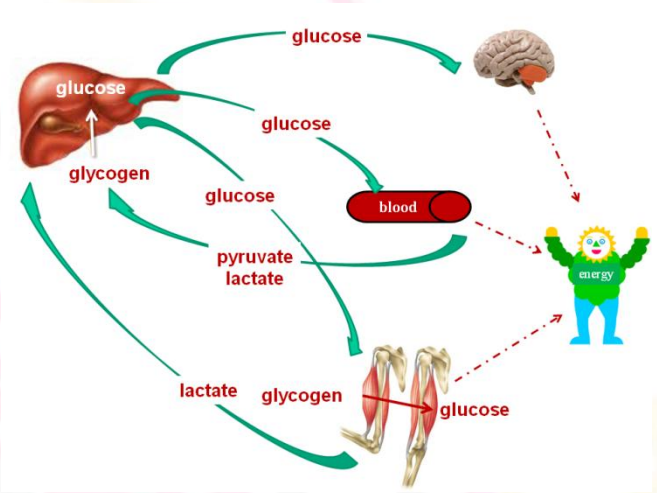



**Glycogen mission is to release glucose according to the body needs**, that is, when the body requires the energy provided by glucose degradation.

Glycogen is stored abundantly in the **liver** and, to a lesser extent, in the **skeletal muscle** and other tissues, such as the brain.

The **glycogen stored in the liver is converted to glucose by glycogenolysis,** and glucose is released into the blood to keep **glycemia** (free glucose concentration in the blood), being used by all tissues that are unable to generate sufficient glucose for its energy needs.

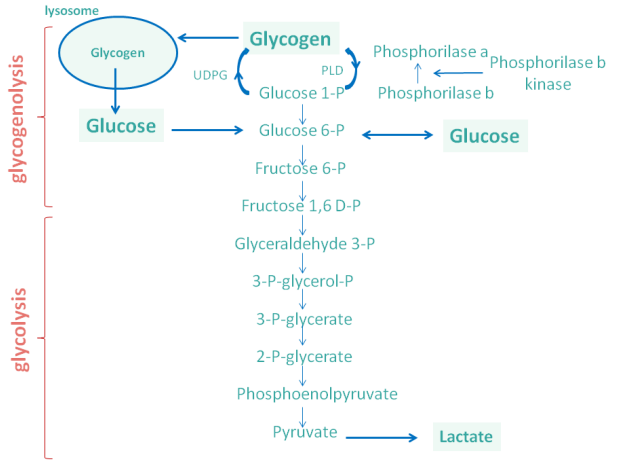
By contrast, **glycogen stored in the muscle is a source of energy for muscle cells** that store it.




## HOW DOES THE LIVER GLYCOGEN METABOLISM WORK?

Glycogen is synthesized and degraded by a highly regulated series of enzymatic reactions. They are summarized in the diagram below.

The first part of the degradation process involves the conversion of glycogen to glucose and is known as **glycogenolysis**, while the subsequent conversion of glucose to pyruvate is known as **glycolysis**.




## WHY DO GLYCOGENOSIS OCCUR?

Any defect in the proteins involved in glycogen metabolism or its regulatory mechanisms may cause an alteration of this metabolism leading to excessive accumulation, abnormal or deficient synthesis. All these proteins are **genetically determined** (encoded), so that **mutations** (stable and heritable changes) in the genes

that encode them may alter the correct synthesis of these proteins and, therefore, its structure and function, causing alterations in glycogen metabolism that have clinical and biochemical consequences, known as **glycogen storage diseases**.

The two most affected tissues when a defect in glycogen metabolism occurs are those where this metabolism is more active, **liver and muscle**. We are dealing with liver and muscle glycogen storage diseases in two different sections.


## WHAT ARE MUSCULAR GLYCOGEN STORAGE DISEASES?

Muscular GSD are the goup of hereditary diseases affecting the metabolism of glycogen stored in the muscle. Generally, they are caused by the deficiency of enzymes involved in the metabolism of muscle glycogen. They can cause:

- Excessive accumulation of glycogen molecules with normal structure.
- Excessive accumulation of glycogen molecules with abnormal structure.
- Glycogen depletion, that is, the absence of glycogen synthesis.

They have similar clinical characteristics although its severity and complications are different:

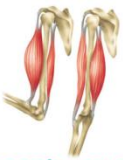
- Exercise intolerance with cramps.
- Myoglobinuria (appearance of myoglobin in urine, which is a muscle protein that gives urine a cognac color).
- Progressive weakness. We will treat them as a whole, except for Pompe disease (GSD-II) which will be discussed further in another section.

### Clinical features of muscular GSD


Exercise intolerance


Cramps

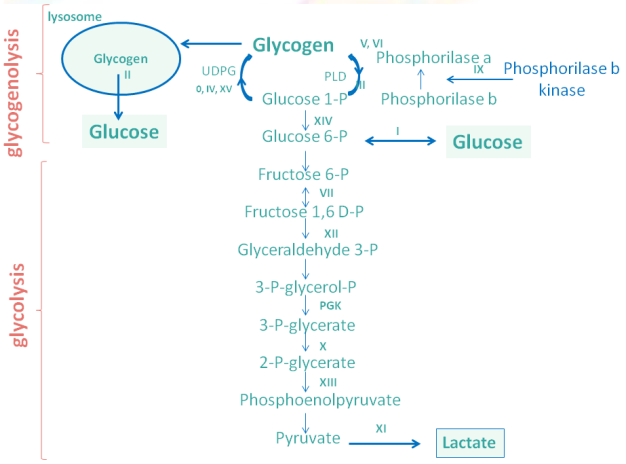

Myoglobinuria


Progressive weakness

## WHAT ARE THE MAJOR MUSCLE GLYCOGENOSIS?

Nowadays these group of diseases are identified by Roman numerals, related syndromes to the first clinical description and the names of the deficient enzyme proteins in each disease. The new pathophysiological classification (Gazzerro E. et al, *Curr Neurol Neurosci Rep* 2013; 13:333) distinguishes between:

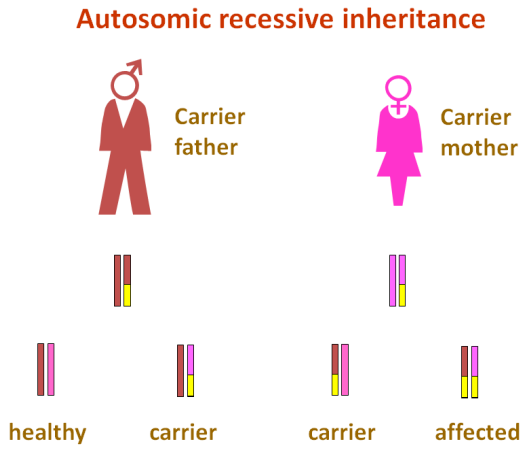
- **Primary Glycogenosis:** caused by genetic defects in the enzymes directly involved in the synthesis of glycogen (gluconeogenesis), degradation (glycogenolysis) and glucose metabolism (glycolysis).
- **Secondary Glycogenosis:** caused by the loss of function of regulatory proteins that indirectly affect the enzymes involved in the glycogen and glucose pathways.



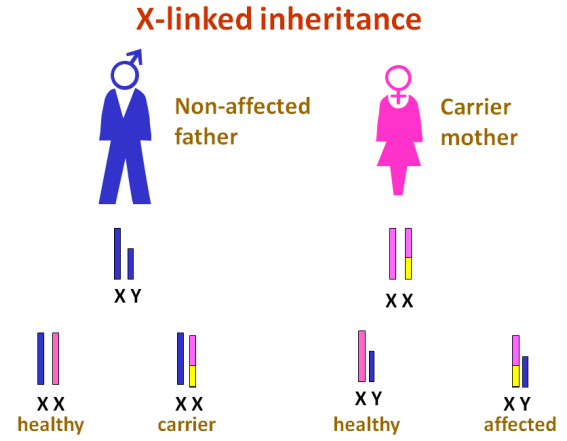

In the attached figure, muscle glycogenosis are primarily indicated in green while primarily liver glycogenosis are indicated in red color. Many enzymes have liver and muscle isoforms, and therefore, clinical features express in both organs (GSD III, IV, IX, 0).

## HOW ARE LIVER GLYCOGENOSIS INHERITED?

These deficiencies are genetic disorders mainly **inherited as autosomal recessive diseases**, i.e., parents carry mutations in one of these genes, but do not suffer the effects of the enzyme deficiency. If both parents transmit the mutation to the child, he/she will suffer a **glycogenosis**.




There are some forms of muscle glycogen storage diseases (GSD-VII and IX) whose genes are located on the X chromosome, so that the **inheritance will be X-linked**, i.e., maternal inheritance.




## WHAT ARE THE MAIN CLINICAL FEATURES OF MUSCLE GLYCOGEN STORAGE DISEASES?

The main clinical features of primary muscle GSD are summarized in the following table (modified Gazzerro E et al, Curr Neurol Neurosci Rep 2013, 13:333).

The most frequent GSD within this group are GSD-II,GSD-III, and GSD-V, and GSD-VII. The GSD-II is specifically addressed in another section.

**GSD-III** is caused by amylo 1,6-glucosidase or debranching enzyme deficiency, whose mission is to break α-1, 6 glucosidic linkages of glycogen. Its deficiency causes dextrin accumulation, reducing glucose release. It can manifest in liver, heart and muscle (GSD-IIIa) or only in liver (GSD-IIIb). The GSD-IIIa is expressed in muscle in the third or fourth decade of life with exercise intolerance, muscle weakness and elevated creatin kinase (CK) levels. Cardiac involvement is most evident by ultrasound procedures and more variable by symptoms, and can be silent for many years.

| Primary GSD | Enzymatic defect (gene) | Clinical features |
|---|---|---|
| II, Pompe | Acid α-glucosidase (*GAA*) | Infantile: cardiomegaly, hepatomegaly, hypotonia<br>Juvenile & adult: progressive weakness |
| III, Cori | Debranching enzym (*AGL*) | Infance: hypotonia, weakness, hepatomegaly, cardiopathy, hypoglycemia. Adult: progressive weakness |
| IV, Andersen | Branching enzym (*GBE1*) | Congenital: hypotonia, hepatic failure<br>Juvenile & adult: proximal weakness, APBD* |
| V, McArdle | Myophosphorilase (*PYGM*) | Exercise intolerance, myalgia, cramps<br>Tardia: myoglobinuria, weakness |
| VII, Tarui | Phosphofructokinase (*PFKM*) | Exercise intolerance, myalgia, cramps, myoglobinuria, weakness, hemolytic anemia? |
| IX | Phosphorilase kinase (*PHKA1*) | Exercise intolerance, myalgia, cramps, myoglobinuria, weakness, hepatopathy? cardiopathy? |
| PGK | Phosphoglycerate kinase (*PGK1*) | Exercise intolerance, myalgia, cramps, myoglobinuria, weakness, hemolytic anemia, epilepsy |
| X | Phosphoglycerate mutase (*PGAM2*) | Exercise intolerance, myalgia, cramps myoglobinuria, weakness |
| XI | Lactate dehydrogenase (*LDHA*) | Exercise intolerance, myalgia, cramps myoglobinuria, weakness, acroeritema |
| XII | Aldolase(**ALDO-A**) | Exercise intolerance, weakness & hemolytic anemia ? |
| XIII | β-enolase (*ENO*) | Exercise intolerance, weakness |
| XIV | Phosphoglucomutase (*PGM-1*) | Exercise intolerance, myoglobinuria |

**GSD-V or McArdle disease** is caused by myophosphorylase (muscle phosphorylase) deficiency. Some signs appear in childhood but often it is not diagnosed until the 2nd or 3rd decade of life. It presents with exercise intolerance, myalgia (muscle pain) and muscle stiffness or weakness in action that improves with rest. Intense exercise is poorly tolerated, causing painful cramps and spasms. A characteristic phenomenon is the 2nd pulse (* see table), which consist of after a decrease in the intensity of exercise, the patient returns easier because of the body's ability to find alternative energy sources, such as fatty acids .

**GSD-VII or Tarui disease** is caused by deficiency of the muscle subunit of phosphofructokinase (PFK-M), the first step of glycolysis that converts fructose 6-phosphate to fructose 1,6 diphosphate. The most common adult form is manifested by muscle cramps and exercise-induced weakness and myoglobinuria, and hyperbilirubinemia (increased bilirubin in the blood), compensated hemolysis (breakdown of red blood cells). A less common infantile form, with generalized weakness and involvement of other organs present with seizures,

cortical blindness, corneal opacities and cardiomyopathy.

The main clinical features of muscle GSD causing glycogen depletion and secondary GSD are summarized in the following table (modified from Gazzerro E et al, *Curr Neurol Neurosci Rep* 2013, 13:333).

**Clínical features of glycogen depletion and secondary GSD**

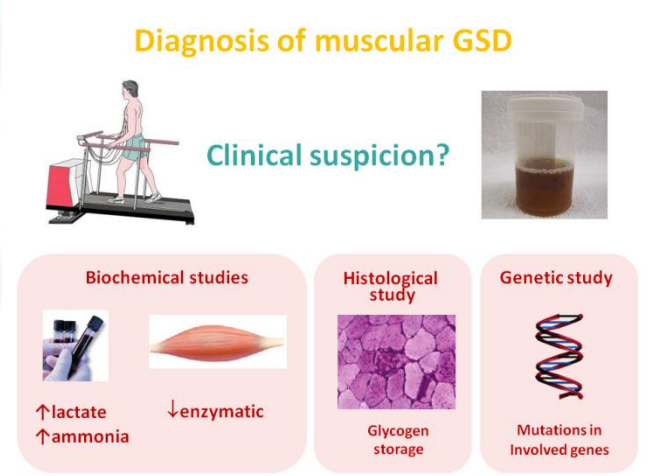
| GSD | Enzymatic defect (gen) | Clínical features |
|---|---|---|
| **Depletion** | | |
| XV | Glycogenin (***GYG1***) | Weakness, hypertrofic cardiomiopathy? |
| 0 | Glycogen sinthase (***GYS1***) | Exercise intolerance, cardiac arrhythmia? |
| **Secondary** | **Protein defect (gen)** | |
| FCNHG FHC/WPWS | AMPK (***PRKAG2***) | Massive cardiomegaly hypertrofic cardiomiopathy with WPWS |
| Lafora disease | Laforin (***EPM2A***) | Progressive myoclonic epilepsy |
| | Malin (***EPM2B***) | Exercise intolerance, myalgia, cramps, myoglobinuria, weakness, hemolytic anemia, epilepsy |

## HOW ARE MUSCLE GLYCOGENOSIS DIAGNOSED?

The diagnosis is based on clinical exercise intolerance, myoglobinuria with cramps, and progressive weakness.

Dynamic tests such as ischemic exercise test on the forearm provide important data for the differential diagnosis of McArdle disease (GSD-V) and other muscle GSD or other diseases. A positive ischemic stress test (absence of elevated lactate but elevated ammonium after ischemic stress) is suggestive of GSD-V, while if ammonia does not rise could indicate that the effort has been inadequate.

Muscle biopsy shows glycogen deposits and allows the demonstration of the enzyme defect.




Genetic testing is required for final confirmation of the muscle GSD and allows genetic counseling and prenatal diagnosis if required.

## IS THERE A TREATMENT FOR MUSCLE GLYCOGEN STORAGE DISEASE?

There is no specific treatment for muscle GSD, except for GSD II or Pompe disease (treated extensively in another section).

In general, to avoid violent exercise is recommended as a preventive measure.

In GSD-V or McArdle moderate aerobic training, based on the "second wind" phenomenon is recommended.

Muscle GSD are potentially serious diseases, but diagnosis and preventive measures improve the quality of life of individuals who suffer them.

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