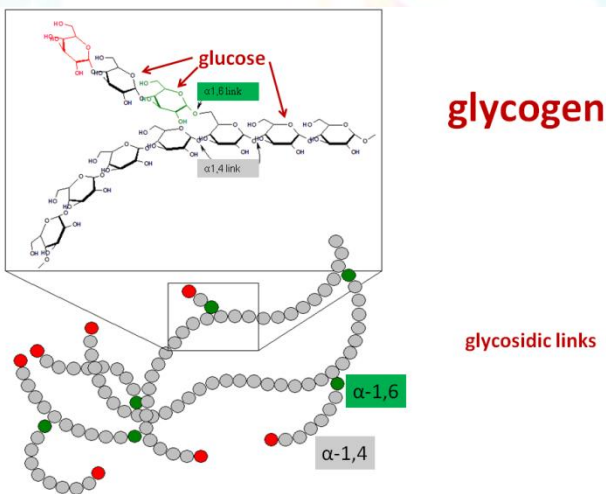


HEPATIC GLYCOGENOSIS

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.

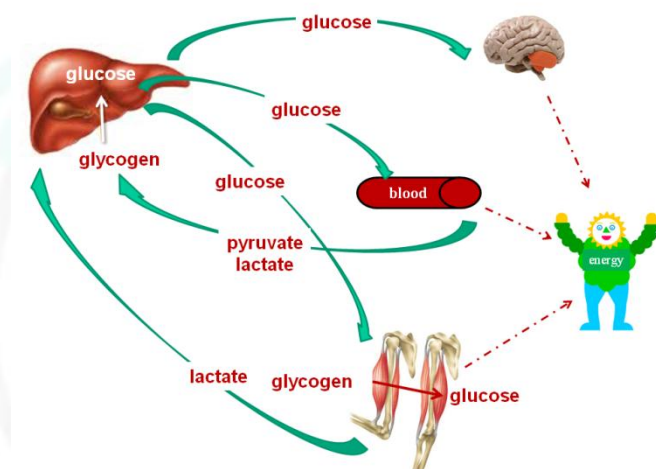
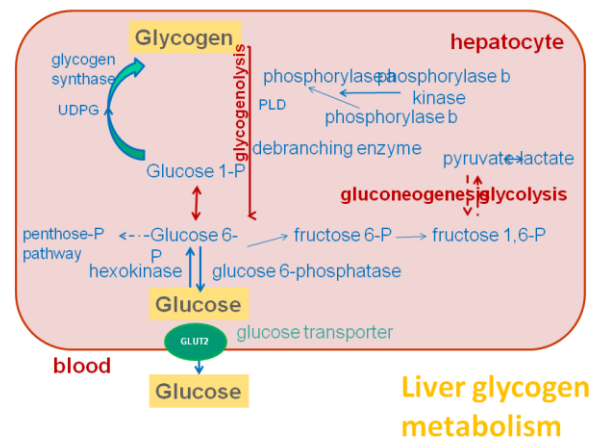
Glycogen is stored abundantly in the liver and, to a lesser extent, in the skeletal muscle and other tissues, such as the brain.

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.

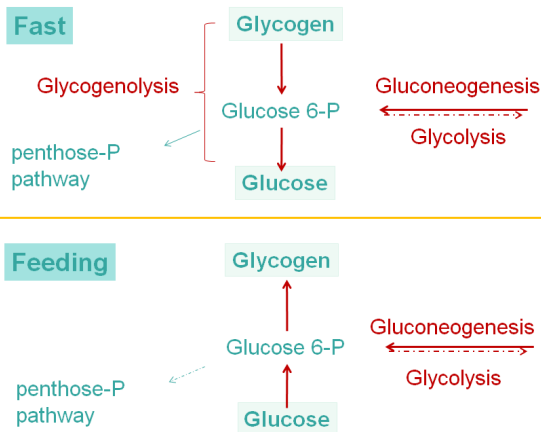


Glycogen mission is to release glucose according to the body needs, that is, when the body requires the energy provided by glucose degradation.

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**. The inverse transformation of pyruvate to fructose 1,6-diphosphate to form glucose again is called **gluconeogenesis**.

These non-reversible pathways (one-way function) are regulated by hormones and other activating or inhibitory enzymes, depending on the energy requirements. During prolonged fasting starts glycogenolysis and gluconeogenesis to maintain blood glucose homeostasis (blood glucose). After feeding,

the gluconeogenesis is still active, in this case for the synthesis of glycogen from glucose.



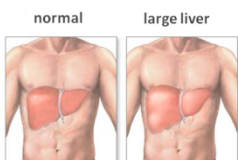
WHY DO GLYCOGENOSIS OCCUR?

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 LIVER GLYCOGENOSIS (GSD)?

Clinical features of hepatic glycogenosis



hepatomegaly



hypoglycemia



grown retardation

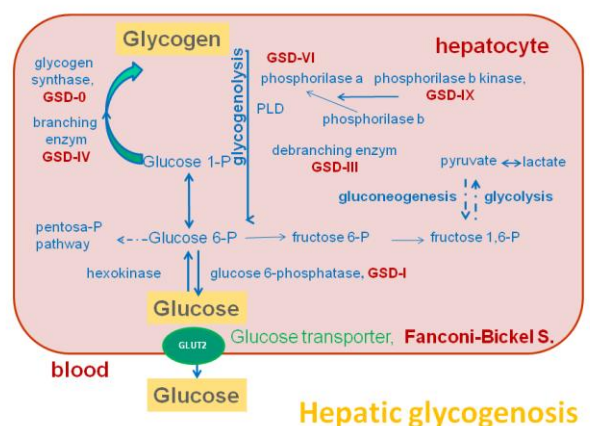
They are the **group of hereditary diseases affecting the metabolism of glycogen stored in the liver**. Generally, they are caused by **deficiencies of enzymes involved in hepatic glycogen metabolism**. Liver GSD will be treated as a whole, because they have similar clinical characteristics (**hepatomegaly, hypoglycemia and growth retardation**), although their severity and complications are different.

WHAT ARE THE MAJOR HEPATIC GLYCOGEN STORAGE DISEASES?

Hepatic Glycogenosis (GSD)

GSD type, disease name	Enzymatic or transporter defect (gene)	Affected organ
Ia, von Gierke	Glucose-6-phosphatase (G6PC)	Liver, kidney
Ib	Glucose 6-phosphatase traslocase (SLC37A4)	Liver, kidney, leukocytes
III, Cori, Forbes	Debranching enzyme (AGL)	Liver, muscle
IV, Anderson	Branching enzyme (GBE1)	Liver
VI, Hers	Phosphorilase (PYGL)	Liver
IX	Phosphorilase-β-kinase (PHKA2)	Liver and/or muscle
0	Glycogen synthase (GYS2)	Liver,
Fanconi-Bickel syndrome (secondary GSD)	GLUT2 transporter (SLC2A2)	Liver, kidney

They are named by Roman numbers, related syndromes, and the first clinical description with the names of the deficient enzyme proteins in each disease. These names, as well as the organs primarily affected in them are summarized in the accompanying Table. In the Figure, liver glycogenosis are labelled in red.

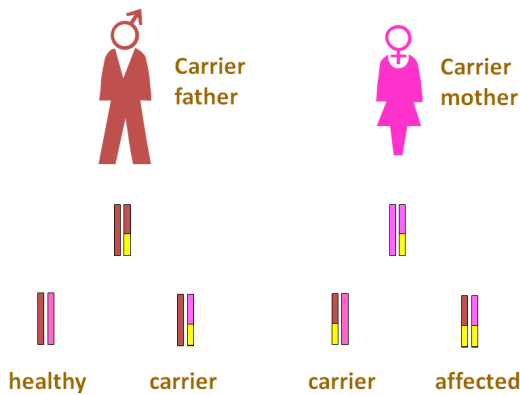


HOW ARE LIVER GLYCOGENOSIS INHERITED?

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

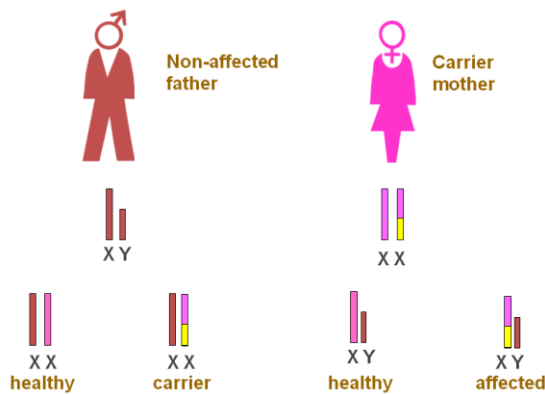
transmit the mutation to the child, he/she will suffer a glycogenesis.

Autosomal recessive inheritance



A form of glycogen storage disease (GSD IXa) is X-linked, ie, shows **maternal inheritance**.

X-linked inheritance



WHAT ARE THE MAIN CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF LIVER GLYCOGEN STORAGE DISEASE?

All hepatic glycogen storage diseases are clinically characterized by **hepatomegaly and growth retardation**, but the hepatic involvement is very serious in **GSD-Ia**, caused by **deficiency of glucose 6-phosphatase**, since the defect prevents the formation of glucose from glucose 6-P. The hepatopathy may appear already at birth or in the neonatal period and is accompanied by severe hypoglycemia, lactic acidemia, metabolic acidosis, hyperuricemia and hyperlipidemia.

The **GSD-Ib variant** is caused by **deficiency of the translocase of glucose 6-phosphate** to the endoplasmic reticulum, where glucose 6-phosphatase converts glucose 6-P into glucose, which then enters the bloodstream. The GSD-Ib, which has the same

biochemical features of GSD-Ia, also presented with **neutropenia** (decreased number of neutrophils in the blood) ranging from mild to agranulocytosis (significant decrease in the number of neutrophils), which determines the appearance of oral or intestinal ulcers.

GSD-III is caused by **deficiency of amyl 1,6-glucosidase or debranching enzyme** (break α -1, 6 glycosidic links). There are more frequent variants with liver and muscle involvement (IIIa) or single hepatic expression (IIIb). The clinical expression is milder than that of GSD-I and patients tolerate better fasting.

GSD-IV or amylopectinosis is caused by the **branching enzyme deficiency** which causes the accumulation of abnormal unbranched glycogen like amylopectin (polyglucosan: glucose polymer) which accumulates in tissues causing cellular damage. The GSD-IV occurs between 3-15 months with hepatomegaly, failure to thrive and abdominal distension, and can lead to chronic liver disease (cirrhosis). There are few variants with multisystem involvement, affecting the liver and muscle, also presenting hypotonia and cardiomyopathy.

Hepatic glycogenesis

GSD type	Clinical features	Biochemical abnormalities
Ia, von Gierke	Hepatomegaly +++, delayed growth	Hypoglycemia +++, lactic acidemia, uricemia++, lipidemia, mild ketosis
Ib	Hepatomegaly, delayed growth, neutropenia, oral and intestinal ulcers	Hypoglycemia +++, lactic acidemia, uricemia++, lipidemia, mild ketosis
III, Cori, Forbes	Hepatomegaly, delayed growth	Hypoglycemia, ketosis++, hyperlipidemia, \uparrow CK, \uparrow transaminases
IV, Andersen	Hepatomegaly, delayed growth, abdominal distension, cirrhosis	Hypoglycemia infrequent
VI, Hers	Hepatomegaly, delayed growth, Abdominal distension	Hypoglycemia, mild ketosis
IXa, c	Hepatomegaly, delayed growth (GSD-Ixa: X-linked inheritance)	Hypoglycemia, mild ketosis, mild hyperlipidemia
IXb	Hepatomegaly, delayed growth Hypotonia, muscular weakness	Hypoglycemia, mild ketosis, mild hyperlipidemia
Fanconi-Bickel S.	Hepatomegaly, Fanconi tubulopathy, delayed growth	Hypoglycemia (fast), glycosuria, hyperaminoaciduria, acidosis, hyperphosphaturia,...

The defects of the **liver phosphorylase system** include the **liver phosphorylase deficiency (GSD VI)** and **phosphorylase kinase deficiency (GSD-IX)**. Phosphorylase breaks glycogen linear chains to produce glucose 1-P, but must be activated by the action of phosphorylase kinase, i.e. they act in concert. Liver forms of both defects are similar, lighter than the previous ones and with better clinical prognosis. GSD-IX has 6 subtypes, being the hepatic form GSD IXa (of X-linked inheritance and the most common), GSD IXc (not X-linked) and GSD-IXb, with expression in liver and muscle.

The **hepatic isoform of glycogen synthase deficiency or GSD-0**, is caused by a defect in the ability to accumulate glycogen and presents without enlarged liver, although short stature and ketotic hypoglycemia are present.

Finally, **GLUT2 deficiency**, although it is an impaired glucose transport, has clinical features similar to GSD with impaired glycogenolysis and gluconeogenesis (formation of glucose from pyruvate). Clinical manifestations appear between 3-10 months and consist of hepatomegaly, Fanconi tubulopathy (glycosuria, hyperphosphaturia, hyperaminoaciduria).

HOW ARE LIVER GLYCOGENOSIS DIAGNOSED?

Diagnosis of glycogenosis



Clinical suspicion?



Biochemical studies



↓ glucose, ↑ lactate
↑ ketone bodies
↑ uric a., triglycerids



renal
function



↓ enzymatic



Genetic study



**Mutations in
involved genes**

Diagnosis is based on clinical features: **hepatomegaly, growth retardation and hypoglycemia**. Biochemical determinations of glucose, lactate, ketone bodies, liver function, uric acid, lipid metabolism (cholesterol and triglycerides), blood count and dynamic tests (oral glucose, glucagon and galactose curves) provide data for the differential diagnosis between the GSD. Imaging techniques and liver biopsy show increased liver glycogen and the presence of fat (steatosis), fibrosis or cirrhosis.

The **biochemical diagnosis** is confirmed by demonstration of the enzymatic defect in erythrocyte or liver biopsy, and the **genetic study** is essential for genetic counseling and prenatal diagnosis, if required.

IS THERE TREATMENT FOR HEPATIC GLYCOGEN STORAGE DISEASE?

In most cases the treatment aims at preventing hypoglycemia with dietary measures (frequent meals, introducing carbohydrates with prolonged absorption, etc.) (See Tips: How to delay glucose absorption, How to use a blood glucose meter).

Usually the prognosis is good if the proper controls and monitoring are performed.

Some types of glycogen storage such as GSD-I may have renal and bone complications, to be followed closely. It is also common growth retardation, in some cases, which can be prevented with proper nutrition.

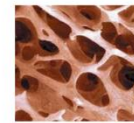
Liver transplantation is indicated in some serious forms that do not respond well to nutritional therapy and tend to lead to cirrhosis (GSD-I, III or IV).

Treatment of hepatic glycogenosis

Prevention



hypoglycemia



osteopenia



delayed
growth

- Dietetic-nutritional treatment
- Carbohydrates of delayed absorption
- Nocturnal infusion of glucose polymers
- Vitamin and mineral supplements

Liver glycogenosis are potentially severe diseases if not diagnosed and treated properly. However, early diagnosis and treatment greatly improve the quality of life of patients who suffer them.

Translation

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