

# Glycogen Storage Diseases

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## Type I Glycogen Storage Disease Type I GSD

### Synonyms:

von Gierkes disease, Type I Glycogenosis, Hepatorenal Glycogenosis  
Type I Glycogen Storage Disease accounts for about 25% of all cases of GSD diagnosed in the USA and in Europe and has an estimated incidence of about 1 in 100,000 live births.

In Type I Glycogen Storage Disease (GSD I), the most frequent first symptoms include an enlarged liver and low blood sugar (hypoglycemia). After we eat, excess glucose is stored as glycogen mostly in the liver to be used later when we are fasting (not eating for 3-4 hours) to maintain normal glucose levels in our body. In GSD I the metabolic problem is centered in the liver because the enzyme needed to release glucose from glycogen is missing.

There are two different subtypes of Type I Glycogen Storage Disease – called type Ia and type Ib. GSD Ia is caused by a deficiency of the glucose-6-phosphatase (G6Pase) enzyme in liver, kidney and other organs of the body. GSD Ib is caused by a deficiency in glucose-6-phosphate translocase, or transporter (G6PT) enzyme, that helps in transporting G-6-Pase enzyme from one point to another. These two enzymes work together to help the body break down the storage form of sugar (glycogen) in to free glucose (sugar) for use when we are not eating. When a person does not have enough of either of these two enzymes, they usually have many of the same signs and symptoms early on in life.

Individuals with Type I Glycogen Storage Disease are unable to release glucose from glycogen mainly in the liver (see [What is a Glycogen Storage Disease?](#)). They cannot maintain their blood glucose (sugar) levels and within a few hours after eating they will develop hypoglycemia (low blood sugar). The low levels of glucose in the blood of these individuals often result in chronic hunger, fatigue,

and irritability. These symptoms are especially noticeable in infants. Symptoms of hypoglycemia often appear when the time between feedings increases and the infant sleeps through the night. In infants, children and adults, symptoms may also be present when an illness prevents normal feeding routine and time. If the blood sugar is very low, some individuals may have seizures (hypoglycemic seizures).

Since people with Type I GSD are able to store glucose as glycogen but not able to release it normally, with time the stores of glycogen build up in the liver causing the liver to swell (hepatomegaly). This is much like being able to place groceries from the store into your kitchen cabinets, but not being able to get the food out of the cabinets when needed. Levels of hormones, lactic acid, triglycerides, lipids (fats), uric acid and other by-products of metabolism increase in the blood as the body tries to raise blood sugar. Fats get stored in the liver along with the glycogen, which leads to the enlargement of the liver. The liver does its many other functions normally, and there is not usually any evidence of liver failure. The kidneys are also enlarged due to increased glycogen storage.

The continued presence of low blood sugar can eventually lead to delayed growth and development as well as abnormal levels of some metabolites (substances) in the blood and urine. High blood pressure has also been seen in a number of individuals and when this occurs, appropriate treatment is needed.

In addition to the problems described above, individuals with Glycogen Storage Disease Type Ib can develop frequent bacterial and fungal infections, due to abnormal functioning of the white blood cells called neutrophils. These are the fighter cells of the body. Therefore, people with GSD Ib can have low levels of neutrophils in their blood (a finding called neutropenia). Many people with GSD Ib use a medicine called G-CSF to increase the number of neutrophils in the body. People with Glycogen Storage Disease Type Ib may also develop chronic pancreatitis, chronic inflammatory bowel disease, and Crohn's disease.

The diagnosis of Type I GSD will always include blood studies such as blood glucose, cholesterol, triglycerides, lactate, and uric acid, measurements of growth, and ultrasound or other imaging studies to measure the size of the liver and kidneys. By looking for changes in the genes associated with GSD I, genetic (DNA) testing can be used to diagnose the majority of individuals with GSD Type Ia and Ib. Sometimes liver biopsy analysis will be needed to examine the enzyme levels of someone suspected to have Type I Glycogen Storage Disease, especially in situations when DNA testing is negative and the clinical suspicion of GSD I is high.

The treatments of Type I Glycogen Storage Disease are aimed at correcting the metabolic changes in the body and promoting growth and development. Current treatments consist of providing small, frequent feedings during the day. Most agree that fructose and galactose should be restricted, but the degree of restriction is still debated. The restriction of these sugars translates to no fruit, juice, table sugar, cake, pie, syrup, jelly, honey, and candy; and limited amounts of dairy foods including milk, yogurt and cheese. The majority of medical centers recommend the use of uncooked cornstarch, mixed in water, soy formula or soy milk (sucrose, fructose and lactose free). Cornstarch should not be mixed in drinks that contain high amounts of ascorbic or citric acid and the cornstarch drink should not be heated as this may alter its structure rendering it less effective. Cornstarch is digested slowly so it provides a steady release of glucose in between feedings. In some cases, an overnight tube feeding is required to provide a continuous delivery of glucose. Formulas should be sucrose, fructose and lactose free. The rate of the tube feeding is based on the liver's normal glucose delivery rate and the age and weight of the child. Due to the many restrictions for the GSD I diet, it is necessary to supplement the diet with a multivitamin. Additional calcium supplementation may also be required. Because the diet for Type I Glycogen Storage Disease is complex, the ideal team should include a dietitian and a physician familiar with the long-term care and maintenance related to GSD I.

Patients with Type I Glycogen Storage Disease may develop benign tumors in the liver called hepatic adenomas. Adenomas are usually first noted around the time of puberty. They typically do not cause symptoms and are identified by routine imaging studies of the liver. In rare instances these can develop into liver cancer.

Renal (kidney) disease is another complication in GSD I patients, and most patients with type I glycogen storage disease older than age 20 yr have proteinuria (proteins excreted in urine). Many also have hypertension (high blood pressure), and kidney stones, among other changes in kidney functions. More severe kidney injury may occur with large amounts of protein in the urine, high blood pressure, and decreased ability of the kidneys to filter waste products due to damage to the filtering units of the kidney (glomeruli). In some patients with the advancement of renal/kidney disease, kidney failure can happen which can require dialysis and eventually kidney transplantation.

Other complications can include pulmonary hypertension, radiographic (X-ray) evidence of osteopenia (weak bones), and fractures.

In the past, many patients with Type I Glycogen Storage Disease did not survive infancy and childhood. Today, maintenance of normal or near normal blood sugar/glucose levels with effective therapy improves the metabolic abnormalities and reverses the severe growth failure characteristic of the untreated patients. It is still unclear whether long-term complications can all be prevented by dietary therapy. However, with earlier diagnosis, appropriate diet, and better metabolic control, many individuals with GSD I are doing very well and many adults are living longer and healthier lives.

## Type II Glycogen Storage Disease Type II GSD

Synonyms:

Acid Maltase Deficiency (AMD), Pompe Disease

Pompe disease (Type II GSD) is an autosomal recessive genetic disease that is caused by a lack of function of the enzyme acid alpha-1,4-glucosidase [also called acid maltase]. Type II Glycogen Storage Disease also belongs to a group of metabolic diseases called lysosomal storage disorders (LSDs). Type II GSD is part of both groups because the acid maltase enzyme works in a compartment of the cells in our body, called the lysosomes.

Just as the body is divided into organs, each with its own specific function, the cells themselves are divided into compartments called organelles. There are a number of different organelles in cells. When discussing Pompe disease, our interest is in an organelle called the lysosome. In different parts of the body, lysosomes are found in varying amounts in varying sizes. Lysosomes always consist of a central space filled with material that is completely enclosed by a membrane.

Lysosomes act as tiny garbage collectors in the cell. They keep cells working well by collecting anything that there is too much of in the cells. The substances they collect are then recycled into smaller parts and released into the cell again to be reused or disposed out of the cell. In Type II GSD disease the problem is in breaking down of complex sugars (glycogen) that is in the lysosomes, into simple, easy to digest sugar (glucose) due to the defect in the enzyme called acid alpha glucosidase (GAA).

Without the proper function of this enzyme, the glycogen that enters into the lysosomes is not broken down, but continuously builds up and disrupts the normal functions of the lysosome. This means that in

Pompe disease (Type II GSD disease), where there is no enzyme to break down the glycogen in the lysosomes, that the lysosomes in the heart (also known as cardiac muscle) and other muscles quickly accumulate large deposits of glycogen. Over time these large deposits of glycogen cause the lysosomes to grow larger and larger and eventually breakdown, thus disrupting the function of the cell and organs that the cells make up, in this case the heart and muscles.

GSD Type II is often divided into subtypes based on the age at which the disease first occurs, the severity of the disease and the rate at which the disease progresses. The amount of acid alpha glucosidase that remains active in individuals with Type II GSD plays a part in determining which type of Type II GSD an individual may have. In general, the more enzyme that is present in individual's muscles, the later the onset of the disease, however there are exceptions.

It is broadly classified into infantile and late onset forms.

Infantile-onset form: With this form, infants usually present during early infancy (4-8 months of age) with weakness and floppiness, are unable to hold up their heads and cannot do other motor tasks common for their age, such as rolling over. The muscles in the arms and legs look typical, but are very weak. Breathing muscles are also weak. The heart muscle thickens (cardiomyopathy) and progressively fails in its blood pumping function. Without treatment, infants with Type II GSD usually die before 12 months of age due to heart failure and respiratory weakness.

Late/late onset forms (this includes juvenile and adult): With this form, the disease has a later onset, usually at an age greater than one or two years of age. It progresses more slowly than the infantile form. A decrease in muscle strength is one of the first symptoms observed. Muscles slowly become weaker, especially the large muscles of the legs, trunk and later the arms. Due to muscle weakness,

walking/climbing stairs becomes difficult. The involvement of the muscle weakness progresses slowly over the years. Some adults with Type II GSD use a wheelchair or other assistance with mobility

Late onset Type II GSD also involves the muscles required for breathing (diaphragm and other muscles that assist with respiration). Over a period of time breathing becomes difficult. Some patients have presented with pulmonary (lung) insufficiency due to respiratory muscle weakness. An early finding is difficulty with nighttime breathing, and this can be an early clue. Difficulty breathing can be evaluated by an overnight sleep study. It may become necessary to use a Bi-Pap or ventilator machine to assist in breathing. Respiratory failure is the most common cause of death in individuals with adult Type II GSD. Heart muscle involvement does not appear to be a significant feature in late onset Type II GSD, but is seen in some individuals (heart rhythm disturbances and heart muscle thickness)

Genetics: Type II GSD is a genetic disorder. This means it is caused by a change in a part of an individual's genetic information. Genetic information is stored on genes. Genes serve as the instruction manual for our bodies. They tell the body how to grow and function. They also determine physical features, such as hair color and eye color. A person has around a 30,000 genes in every cell of their body. Two sets of every gene are inherited, one set from the mother and one set from the father.

If there is a change in the genetic information contained on one of these genes, the body is unable to read the instructions. Therefore, it may cause a difference in the way the body functions. This is similar to having a page missing out of an instruction manual for putting an appliance together. Without that page, one would be unable to properly assemble the appliance and it would not be able to work. The gene responsible for making acid maltase is called the GAA gene. If one copy of the GAA gene is altered but the second copy is not, then the body can follow the instructions on the second copy in order to

produce enough acid maltase enzyme. This is like having a second instruction manual to refer to. When both copies of an individual's GAA gene are altered, the body is unable to read any instructions on how to make the proper amount of GAA/acid maltase enzyme. As a result, the individual has Type II GSD.

Diagnosis and testing: Type II GSD can be diagnosed by determining the activity of the enzyme acid alpha glucosidase. This deficiency can be shown with a specific enzyme testing that can be performed on blood samples, muscle biopsy or cultured cells from a skin biopsy. This type of testing is very specific and available at only a few specialized laboratories in the USA. Genetic testing for mutation finding and gene sequencing for Type II GSD is also available clinically from a limited number of laboratories in the USA. For many families, genetic testing is most helpful in providing additional information for the person with Type II GSD and other family members after the diagnosis is made and confirmed using enzyme (acid alpha glucosidase) testing.

If someone with muscle weakness has a muscle biopsy examined at their local hospital by pathology, testing called histopathology will show a great increase of glycogen of normal structure, and microscopic studies will show increased glycogen enclosed within the lysosomes. This type of testing, while helpful in determining that Type II GSD is a possible diagnosis, is not diagnostic for Type II GSD. In some people with Type II GSD, depending on where the piece of muscle was obtained, the muscle histopathology in the piece of muscle from the muscle biopsy can be normal. If Type II GSD is suspected, then diagnostic testing is needed. These diagnostic tests can either test the function of specific enzyme acid alpha glucosidase or genetic testing looking for changes in the GAA gene can be performed.

#### Treatment:

There is currently treatment available for individuals with Type II GSD. This treatment is called enzyme replacement therapy (ERT). The idea behind enzyme replacement therapy aims to replace the defective acid alpha glucosidase enzyme that people with Pompe disease either cannot make at all or cannot make enough of. It is a synthetic (recombinant, genetically-engineered), form of acid alpha glucosidase. ERT is given to patients as an intravenous (IV) infusion (an injection given over time directly into a vein).

ERT for Type II GSD in the form of a product called Myozyme®. Myozyme® is manufactured and distributed by a company called Genzyme. If you have questions about enrolling in clinical trials or other therapy programs for Pompe disease, contact the Medical Information Department at Genzyme 800-745-4447 in the United States or 617-768-9000 from anywhere in the world

Note: Since there is multisystem involvement and clinical variability, a team approach to medical care is optimal. Individuals with Pompe disease report the best success when they work closely with a coordinating physician, either primary care or specialist, familiar with the likely disease manifestations. Many specific issues related to Type II GSD should be addressed by a physician familiar with the needs of individuals with Type II GSD. For example, if an adult with Type II GSD uses a ventilator for breathing assistance, should be regularly evaluated and treated by a pulmonologist (breathing doctor). The best patient response or outcome is often achieved when the entire care team has an understanding of the unique and complex medical needs specific to individuals with Pompe disease.

Frequently involved specialties include:

- cardiology (infantile onset),
- genetics
- neurology
- pulmonology
- intensive care
- respiratory therapy

- physical therapy
- occupational therapy
- speech / language pathology
- nutrition

## Type V Glycogen Storage Disease Type V GSD

### **Synonyms:**

Muscle Phosphorylase Deficiency, McArdle Disease,  
Myophosphorylase Deficiency

The *phosphorylase enzyme* plays a vital role in the breakdown of glycogen into glucose. In the absence of phosphorylase in muscles, glucose can not be released from the glycogen stored in skeletal muscles to create energy. People with Type V GSD experience problems performing and completing most exercises, especially anaerobic exercises. Because they lack the enzyme to metabolize glycogen, which is the main source of energy for anaerobic activity, their body struggles to find other sources of energy to complete a given activity or exercise. Under these circumstances, the body breaks down muscle when trying to attain energy. This causes many symptoms such as muscle pain, muscle cramping, muscle fatigue, and muscle tenderness. With the breakdown of muscle (rhabdomyolysis) and the release of the red protein myoglobin, myoglobinuria may develop, as evidenced by dark-red or red-brown urine. Serum creatine kinase levels will be greatly elevated.

The physical exam of patients with Type V glycogen storage disease is normal. They complain of painful muscle cramps after exercise. These persons are commonly muscular; they do not have large livers,

and are normal in height. Their liver phosphorylase activity is normal, and they do not have hypoglycemia. A muscle biopsy will show increased concentrations of glycogen, and a deficiency of the phosphorylase enzyme.

At present, there is no specific treatment for this type of GSD. It is very important for patients to exercise only moderately, for extensive exercise can cause considerable muscle breakdown resulting in a great deal of myoglobin in the urine. Large amounts of myoglobin may precipitate in the kidneys and cause temporary kidney failure. Some patients have developed significant muscle problems (myopathies) later in life