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# HEPATIC GLYCOGEN SYNTHASE DEFICIENCY: AN INFREQUENTLY RECOGNIZED CAUSE OF KETOTIC HYPOGLYCEMIA

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## Abstract

The glycogen storage diseases comprise several inherited diseases caused by abnormalities of enzymes that regulate the synthesis or degradation of glycogen. In contrast to the classic hepatic glycogen storage diseases that are characterized by fasting hypoglycemia and hepatomegaly, the liver is not enlarged in GSD0. Patients with GSD0 typically have fasting ketotic hypoglycemia without prominent muscle symptoms. Most children are cognitively and developmentally normal. Short stature and osteopenia are common features, but other long-term complications, common in other types of GSD, have not been reported in GSD0. Until recently, the definitive diagnosis of GSD0 depended on the demonstration of decreased hepatic glycogen on a liver biopsy. The need for an invasive procedure may be one reason that this condition has been infrequently diagnosed. Mutation analysis of the GYS2 gene (12p12.2) is a non-invasive method for making this diagnosis in patients suspected to have this disorder. This mini-review discusses the pathophysiology of this disorder, use of mutation analysis to diagnose GSD0, and the clinical characteristics of all reported cases of GSD0.

### Keywords

Glycogen storage disease type 0; Hepatic glycogen synthase deficiency; Ketotic hypoglycemia; Lactic acid; Mutation analysis; Hyperglycemia

Type 0 glycogen storage disease (GSD0) is caused by deficiency of the hepatic isoform of glycogen synthase. [1] Although GSD0 has been classified as a glycogen storage disease (GSD), this is a misnomer. In contrast to all other types of glycogenoses, which are characterized by increased glycogen storage, deficiency of glycogen synthase causes a marked decrease in liver glycogen content. GSD0 is the only GSD not associated with hepatomegaly, and hypoglycemia typically is milder than in the other types of GSD. [2]

Although the disease was described in 1963, only 20 cases of GSD0 have been reported in the literature. [1,3-9] Confusion regarding the phenotype of the disease and prior dependence on a liver biopsy to establish the diagnosis may account for the apparent rarity of the disorder. There is, however, increasing evidence that GSD0 has been under-diagnosed. In the original description of GSD0, Lewis et al. described a disease associated with severe hypoglycemia, mental retardation, and recurrent seizures. [3] When no other cases had been recognized for 14 years, the existence of GSD0 was doubted, and investigators suggested that deficiency of

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hepatic glycogen synthase is not compatible with life. [10,11] It has become apparent that GSD0 may not invariably be the devastating disorder that was initially described. Many of the problems originally attributed to GSD0 were probably caused by prematurity of the index cases and not by GSD0 *per se*. With the discovery of different tissue-specific isoforms of glycogen synthase, the phenotype began to emerge (Table 1). [6,12] Discovery of the GYS2 gene, which encodes for the liver-specific form of glycogen synthase, has enabled investigators to clarify the clinical characteristics of the disease caused by deficiency of this enzyme. [1]

This review will summarize recent research which suggests that GSD0 is an under-diagnosed entity and will describe the clinical characteristics of the 20 reported cases.

## Pathophysiology

Glycogen is stored principally in the liver and muscle. After a meal, exogenous glucose delivery increases at rates largely determined by the carbohydrate content of the ingested food and the rate of gastric emptying. Endogenous glucose production is suppressed, and excess glucose either is metabolized or stored as glycogen in skeletal muscle and the liver. Glycogen synthase normally catalyzes the formation of α-1,4-linkages that elongate chains of glucose molecules to form glycogen. In GSD0, only glycogen synthesis in the liver is impaired.

Because a substantial fraction of dietary carbohydrate is normally stored in the liver as glycogen [14], inability to synthesize hepatic glycogen causes postprandial hyperglycemia after ingestion of a carbohydrate-containing meal. Glucose and other sugars taken up by the liver in GSD0 are shunted into the glycolytic pathway leading to postprandial hyperlactatemia and hyperlipidemia (Figure 1). Ketotic hypoglycemia develops with fasting. Intact gluconeogenesis and fatty acid oxidation blunt the decrease in blood glucose levels in the postabsorptive period and explains why this disorder is typically milder than the other hepatic glycogenoses. With more prolonged fasting, however, severe hyperketonemia and free fatty acid elevation inhibit release of alanine from skeletal muscle leading to decreased gluconeogenic precursors and worsening hypoglycemia. [15,16]

## Genetics

GSD0 is caused by mutations in the GYS2 gene located on chromosome 12p12.2 and is inherited in an autosomal recessive manner. To date, fifteen different mutations have been documented, including six which have previously not been reported (Figure 2). Of these, 14 mutations are unique within particular families. The only common mutation is in exon 4 (R246X) and has been found in patients of Italian descent both in Europe and in North America. Cases of GSD0 have been identified throughout Europe, North and South America. [1,6,9]

## Presentation

Children with GSD0 are usually asymptomatic during infancy, but weaning from overnight feeds often proves difficult. When overnight feeds are stopped, fasting ketotic hypoglycemia and irritability before breakfast commonly occur. Patients with plasma glucose concentrations of 25 – 40 mg/dL, however, can be relatively asymptomatic because increased plasma ketones, formed from fatty acid oxidation, provide the brain with an alternative fuel. [17] We suspect that this explains why developmental delay has been described in only 22% of children with GSD0, and seizures are uncommon despite the presence of severe hypoglycemia. [9]

Most children with GSD0 are identified incidentally when hypoglycemia is discovered during an evaluation of lethargy associated with a gastrointestinal illness or other period of poor enteral intake. The manifestations of GSD0 are frequently subtle, however, and children may first come to medical attention for evaluation of short stature, failure to thrive, hyperlipidemia, or

elevation of hepatic transaminase levels (Table 2). The postprandial hyperglycemia and fasting ketonuria characteristic of this disorder may be confused with early diabetes mellitus. GSD0 should be considered in any child with asymptomatic hyperglycemia or glucosuria. [9] As a result of the protean nature of GSD0, only 30% of the reported cases of GSD0 were diagnosed before 2 years of age (Table 3).

## Natural History and Prognosis

Whereas overnight hypoglycemia is common in infants and young children, fasting is usually better tolerated with increasing age. [18,19,20] Most children over 7 years of age tolerate a typical overnight fast without development of hypoglycemia, and fasting for up to 18 hours has been reported in teenagers. This improvement in fasting tolerance, however, is not universal, and some children continue to develop hypoglycemia after an overnight fast. [18] Severe hypoglycemia is unusual in older children and adults; however, ketosis remains common in untreated individuals, and most patients report feeling better with continued overnight glucose supplementation. Hypoglycemia remains a problem even in the older population with prolonged fasting, illness, pregnancy, increased activity, or when normal enteral intake is interrupted. [20] In addition, fatigue with exertion is common in untreated individuals, and glucose supplementation improves stamina during sports and other active periods.

There are few reports of adults with GSD0, and the oldest case documented in the literature is 34 years of age. [1] All of the adults with GSD0 have done well, and there is reason to believe that the prognosis is excellent for these patients despite the lack of reported older individuals. A 26-year old with GSD0 gave birth to a healthy term infant, but overnight hypoglycemia and ketonemia developed in the $2^{nd}$ and $3^{rd}$ trimesters when extra supplementation was not provided. [20]

Short stature and osteopenia are common in untreated children, but improve with prevention of hypoglycemia, lactic acidosis, and ketosis. The long-term complications commonly seen in the other forms of glycogen storage disease, such as hepatic adenomas, cirrhosis, kidney dysfunction, and muscular abnormalities, have not been reported in adolescents or adults with GSD0. In the absence of formal guidelines for long-term surveillance of patients with GSD0, we have, for the present time, undertaken to perform annual abdominal ultrasonographic examinations and screening for nephropathy.

## Diagnosis

Home blood glucose and urine ketone monitoring often is used, initially, to screen for this disorder because fasting hypoglycemia and ketonuria are universal in children less than 5 years of age (Table 4). If fasting ketotic hypoglycemia is demonstrated, testing for post-prandial hyperlactatemia can be performed either using a portable lactate meter at home or by means of an oral glucose tolerance test (with simultaneous measurements of blood glucose and lactate concentrations) after an overnight fast or fasting study (Figure 3). [9] The early morning serum cortisol surge can accentuate the abnormalities. An oral galactose load may also result in increased postprandial blood lactate concentrations. [18] It is important to appreciate that a typical fasting study, which does not measure blood metabolite concentrations in the postprandial period, will often show no obvious hormonal or biochemical abnormalities, leading to misdiagnosis as “ketotic hypoglycemia” or “accelerated starvation”.

Confirmation of the diagnosis has previously depended on a liver biopsy. Despite the decrease in hepatic glycogen content, the response to glucagon is variable and, for poorly understood reasons, may even be near-normal. [5,8] Because there are no clinical laboratories currently assaying activity of the enzyme, a liver biopsy may be inconclusive. Mutation analysis using

DNA extracted from blood or saliva is becoming the gold standard for making the diagnosis ofqq GSD0, and mutation analysis of the GYS2 gene recently became commercially available. A few cases of biopsy proven GSD0 have been diagnosed, however, with no mutations found in the glycogen synthase gene. [unpublished data]

## Treatment

The goal of treatment is to prevent hypoglycemia and to minimize the systemic acidosis by preventing post-prandial lactic acidosis and fasting hyperketonemia. [21] To achieve this objective, patients are treated with a diet high in protein with complex, low glycemic index carbohydrates. Since gluconeogenesis is intact, protein supplementation provides gluconeogenic precursors that can be used for endogenous glucose production. In turn, there is also less dependence upon fatty acid oxidation, and accumulation of free fatty acids and ketones is prevented. This not only reduces systemic acidosis, but prevention of hyperketonemia also enhances gluconeogenesis since more alanine can be released from skeletal muscle. [21] In young children, hypoglycemia may still occur on a high protein diet, and uncooked cornstarch (1-1.5 grams/kg) administered at bedtime, and every 6 hours during illness, prevents morning hypoglycemia and ketosis. Daytime hypoglycemia tends to be mild and frequent snacks, given every 2-4 hours, usually prevents hypoglycemia. In children who are particularly active, a dose of cornstarch in the morning or 1 hour before strenuous or prolonged physical activity can improve stamina. Simple carbohydrates should be limited since they can increase blood lactate concentrations.

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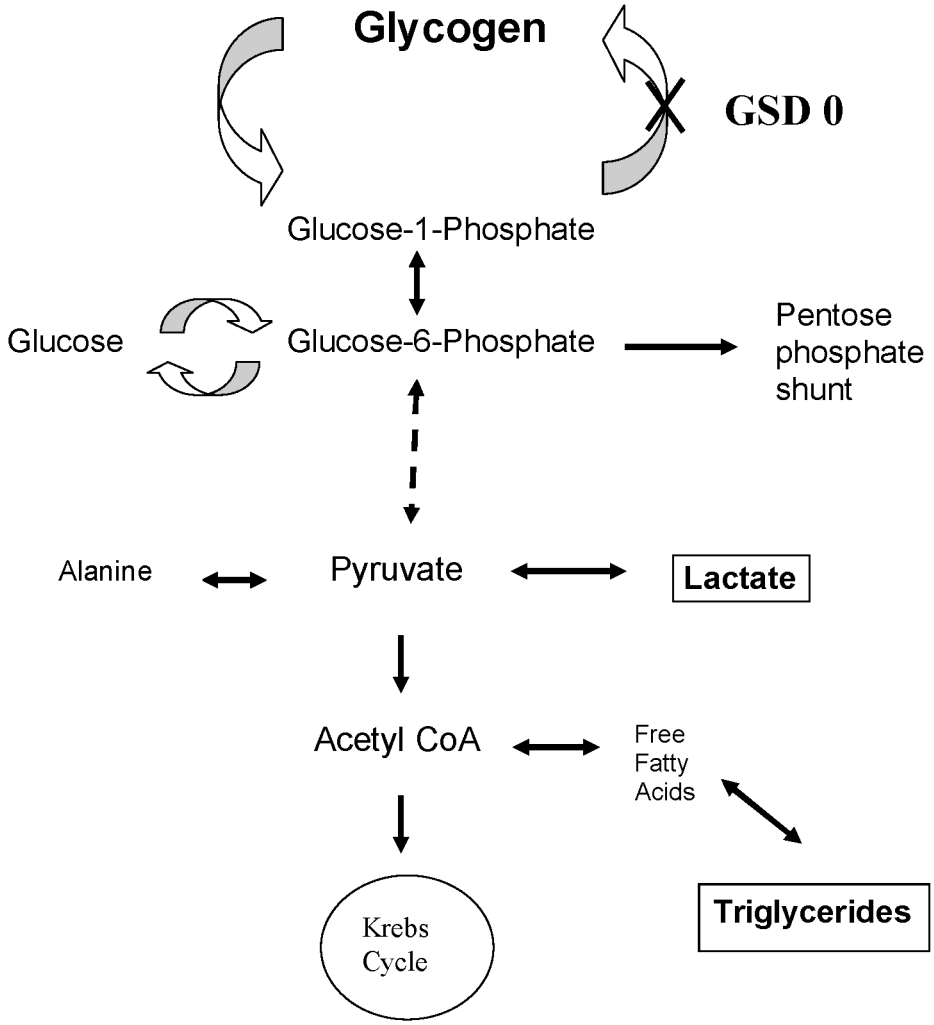


**Figure 1.**
Schematic representation of biochemical pathways affected in glycogen storage disease type 0

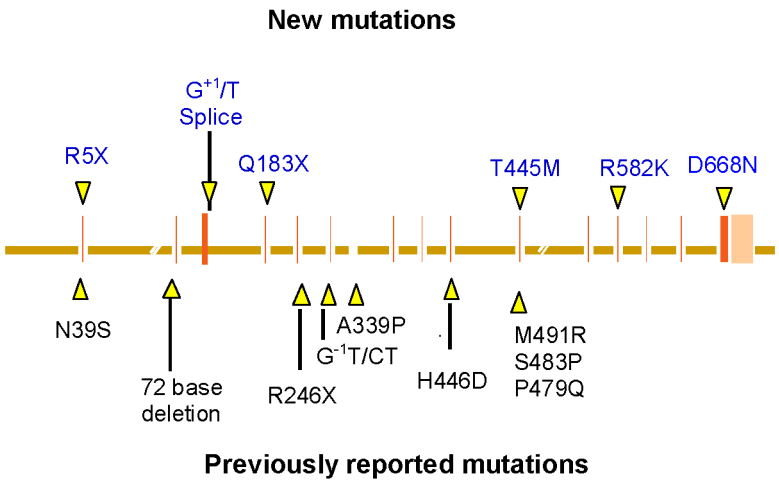


**Figure 2.**
Schematic representation of GYS2 gene with mutations that have been found in patients with GSD0. The gene has 16 exons (represented by the lines), and the arrowheads point to the location of the mutation.

**Figure 3.**
Fasting and feeding study in a subject with mutation proven glycogen storage disease type 0 demonstrating the classic biochemical pattern of fasting hypoglycemia alternating with postprandial hyperlactatemia and hyperglycemia. Symbols represent times of events during the fasting and feeding study: (*) glucagon administration (0.3 mg/kg); (**) mixed meal/ breakfast; and (***) mixed meal/lunch. Adapted from [9], and used with permission from Elsevier Publishers and the Journal of Pediatrics.

## Table 1

**Isoforms of glycogen synthase.** The synthesis of glycogen in liver and muscle is controlled by different isoforms of glycogen synthase. These genes are located on different chromosomes, but share more than 70% homology.

| Characteristic | Hepatic GS | Muscle GS |
|---|---|---|
| Gene | GYS2 | GYS1 |
| Chromosome | 12p12.2 | 19q13.3 |
| Tissues | Liver | Muscle Brain Kidney |
| Clinical Associations | GSD0 | Possible Type II Diabetes PCOS Hypertension |

**Table 2**

Presenting complaint in patients with GSD0.

| **Presenting Complaint** | |
|---|---|
| Seizures | 5/20 |
| Lethargy | 1/20 |
| Hypoglycemia | 2/20 |
| Hyperglycemia | 1/20 |
| Short stature/FTT | 2/20 |
| Hyperlipidemia | 1/20 |
| Glucosuria | 1/20 |
| Family History | 5/20 |
| Unknown | 2/20 |

## Table 3

Demographic data of GSD0 patients at diagnosis.

| **Age (years)** | |
|---|---|
| < 2 | 6/20 |
| 2 - 4 | 5/20 |
| 4 - 6 | 4/20 |
| > 6 | 5/20 |

**Table 4**

Biochemical Features of Subjects with Untreated GSD0.

| Biochemical Features (n=20) | |
|---|---|
| Fasting hypoglycemia | 100% |
| Fasting ketonemia | 100% |
| Postprandial hyperlactatemia | 88-100% |
| Postprandial hyperglycemia | 60% |
| Fasting hypoalaninemia | 88% |
| Mildly elevated serum transaminases | 40% |