Inborn Errors of Metabolism with Hypoglycemia
Glycogen Storage Diseases and Inherited Disorders of Gluconeogenesis

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The brain depends on a continuous supply of glucose because it can neither synthesize glucose nor store more than a few minutes supply as glycogen. Although delivery of glucose to the brain is critical for survival, the total amount of glucose in the blood...
stream can provide energy for the brain for less than 1 hour.\(^1\) Regulation of blood glucose concentrations is, therefore, critical for survival. The body has multiple metabolic pathways (glycogenolysis, gluconeogenesis [GNG], mitochondrial fatty acid oxidation [mFAO], and ketogenesis) controlled by multiple hormones (glucagon, epinephrine, cortisol, and growth hormone), all of which combine to protect against hypoglycemia.\(^2\) The differential diagnosis for hypoglycemia is fairly large, but the primary manifestations are divided into hormonal and metabolic etiologic factors (Table 1). A generalized approach to the evaluation of hypoglycemia is summarized in Box 1 and Fig. 1. This article focuses on the inherited metabolic defects commonly associated with low glucose concentrations: glycogen storage diseases (GSDs) and inherited disorders of GNG.

**PHYSIOLOGY OF FASTING**

The liver plays a central role in maintaining normoglycemia during feeding-fasting transitions. During periods of fasting, the liver changes from synthesizing glycogen to endogenous glucose production by glycogenolysis and GNG. During more prolonged fasting, the origin of endogenous glucose production shifts from mainly glycogenolysis to GNG and the kidney’s contribution increases (Fig. 2).\(^3\)

Following a meal, glucose is predominantly stored as glycogen, a complex, highly branched spherical structure, which allows efficient storage and release of glucose. The liver is freely permeable to glucose, which is rapidly phosphorylated by glucokinase to form glucose-6-phosphate. Following conversion to glucose-1-phosphate, glycogen synthase catalyzes the formation of \(\alpha\)-1,4-linkages that elongate into chains of glucose molecules. A branching enzyme leads to formation of \(\alpha\)-1,6-linkages at approximately every 10 glucose units along the chain. This structure allows for compact storage of glucose and its slow release during periods of fasting. In between meals, a cascade of enzymatic reactions activates hepatic glycogen phosphorylase, the rate-limiting enzyme in glycogenolysis, which removes glucose from the outer branches of glycogen, and leads to formation of glucose-6-phosphate. Hydrolysis

<table>
<thead>
<tr>
<th>Metabolic Causes</th>
<th>Hormonal Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorders of hepatic glucose release:</td>
<td>Hyperinsulinism:</td>
</tr>
<tr>
<td>• Glycogen storage disease types 0, I, III, VI, IX, XI</td>
<td>• Congenital hyperinsulinism</td>
</tr>
<tr>
<td>• Hereditary fructose intolerance</td>
<td>• Exogenous insulin</td>
</tr>
<tr>
<td>• Galactosemia</td>
<td>• Medications</td>
</tr>
<tr>
<td>Disorders of mFAO:</td>
<td>• Insulinomas</td>
</tr>
<tr>
<td>• Carnitine cycle</td>
<td>• Beckwith-Wiedemann syndrome</td>
</tr>
<tr>
<td>• Beta oxidation</td>
<td>• Counter-regulatory hormone deficiency:</td>
</tr>
<tr>
<td>• Ketogenesis</td>
<td>• Growth hormone deficiency</td>
</tr>
<tr>
<td>Disorders of GNG:</td>
<td>• Corticotropin or cortisol deficiency</td>
</tr>
<tr>
<td>• Fructose-1,6-bisphosphatase deficiency</td>
<td>• Panhypopituitarism</td>
</tr>
<tr>
<td>• Pyruvate carboxylase deficiency</td>
<td>• Glucagon deficiency</td>
</tr>
<tr>
<td>• Phosphoenolpyruvate carboxykinase deficiency</td>
<td>• IGF-II production:</td>
</tr>
<tr>
<td>Other metabolic defects:</td>
<td>• Cervical cancer</td>
</tr>
<tr>
<td>• Maple syrup urine disease</td>
<td>• Hepatoblastoma</td>
</tr>
<tr>
<td>• Glycerol kinase deficiency</td>
<td>• Wilms tumor</td>
</tr>
<tr>
<td>• Mitochondrial respiratory chain defects</td>
<td>• Hodgkin lymphoma</td>
</tr>
<tr>
<td></td>
<td>• Other large mesenchymal tumors</td>
</tr>
<tr>
<td></td>
<td>• Glucagon-like peptide secretion:</td>
</tr>
<tr>
<td></td>
<td>• Dumping syndrome</td>
</tr>
</tbody>
</table>

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Box 1  
**Approach for hypoglycemia**

Depending on local situation, resources available, and collaborations, the following steps can be followed. It is important that diagnostics and management go in parallel and to emphasize laboratory studies in stress plasma and urine samples:

1. Before referral to center of expertise:
   a. Confirm hypoglycemia
   b. Analysis of stress samples of blood (lactate, ammonia, blood gas analysis, anion gap, insulin, and cortisol; store a spare plasma sample for later studies) and urine (ketones, store a spare urine sample for later studies), and regular blood samples of transaminases, uric acid, and lipids
   c. Assess:
      i. Family history: including consanguinity, sudden infant death syndrome, growth, hypoglycemias
      ii. Personal history: including detailed feeding history (timing and restrictions, of fruits or protein) and timing of hypoglycemia in relation to feeding moments and intercurrent infections, sleep, seizures, psychomotor development, and newborn screening results
      iii. Physical examination: including dysmorphic features, growth (height, weight, and head circumference) according to target range, liver size
   d. Request additional metabolite studies according to the phenotype in plasma (liver function tests, acylcarnitines, amino acids, asialotransferrins, biotinidase activity) and urine (organic acids, oligosaccharides)
   e. Consider dietary interventions and an emergency regimen based on the phenotype
   f. Controlled fasting studies are not recommended in this phase

2. In center of expertise:
   a. If laboratory studies in stress samples are not available, based on the history, the previously mentioned studies can be requested during an out-patient clinic visit after an overnight fast
   b. Objectify 24-hour glucose concentrations: by 8-point glucose measurements and/or the combination of continuous glucose monitoring plus ketone measurements
   c. Consider dietary interventions and an emergency regimen based on the phenotype
   d. Clear hypothesis for diagnosis?
      i. Yes: targeted enzymatic and/or DNA studies
      ii. No and if there are clinical arguments against idiopathic ketotic hypoglycemia: next-generation sequencing

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**Fig. 1.** Evaluation of hypoglycemia. FFA, free fatty acids; GH, growth hormone; HMG CoA, 3-hydroxy-3-methylglutaryl-CoA.
by glucose-6-phosphatase allows glucose to be released from the liver into the systemic circulation. Debranching enzyme is required for hydrolysis of $\alpha$-1,6-linkages at branch points.4

Although glucose generated from glycogenolysis primarily is used to maintain normoglycemia early in fasting, endogenous glucose production from the gluconeogenic pathways also is important. In GNG, precursors are generated from 4 sources: lactate, pyruvate, glycerol, and alanine. These substrates are converted to glucose through pathways that depend on several key enzymes: pyruvate carboxylase (PC), phosphoenolpyruvate carboxylase, and fructose-1,6-bisphosphatase (FBPase).5 GNG can occur in both the liver and kidney, and renal-derived glucose can account for up to 20% of endogenous glucose production, especially when systemic acidosis is present.6 The percentage of glucose generated from GNG increases with the duration of fasting.

Prolonged fasting increases mFAO flux. With beta-oxidation, fatty acids are metabolized to acetyl coenzyme A (CoA) which can provide energy through the Krebs cycle. Formation of ketones from acetyl CoA by the liver also occurs, and ketones serve as an alternative energy source for the heart, muscles, and brain, thereby decreasing glucose utilization by these tissues.7 The inherited disorders of mFAO will be reviewed in Areeg El-Gharbawy and Jerry Vockley’s article, “Inborn Errors of Metabolism with Myopathy: Defects of Fatty Acid Oxidation and the Carnitine Shuttle System,” in this issue.

HEPATIC GLYCOGEN STORAGE DISEASES

The GSDs comprise several inherited diseases caused by abnormalities of the enzymes and transporters that regulate glycogen synthesis and degradation. Glycogen is stored principally in the liver, muscle, and kidneys. Muscle, however, lacks glucose-6-phosphatase, and is consequently unable to generate glucose for systemic use. Hypoglycemia is the primary manifestation of the hepatic GSDs (types 0, I, III, VI, IX, and

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Fig. 2. Endogenous glucose production with fasting. The major metabolic pathways responsible for glucose homeostasis. The time on the x-axis depends on age and is more compact with younger patients. Specific enzyme or transporter defects in these pathways are associated with fasting intolerance and (recurrent) hypoglycemia. Endocrine disorders are associated with abnormal exogenous carbohydrate (blue) requirements, such as congenital hyperinsulinism, hypocortisolism, and so forth. Other associations include glycogenolysis (green), GNG (red), defects of mFAO (purple), and defects in ketogenesis and ketolysis (yellow).

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XI), whereas weakness and/or muscle cramps are the primary features of the muscle GSDs (types II, III, IV, V, VII, X). Type GSD III is the only type of GSD with concomitant liver and muscle disease. Type IV GSD (branching enzyme deficiency) results in scarring of the liver and cirrhosis in the classic form of the disease. Because hypoglycemia is not a manifestation of GSD IV until liver failure occurs, it is not discussed in this article (Table 2).

**Glycogen Storage Disease Type I (von Gierke Disease)**

Type I GSD is the classic form of the condition due to decreased glucose-6-phosphatase (G-6-Pase) function. There are 2 forms of GSD type I: type Ia and Ib. Type Ia is due to defects in the G6PC gene, which encodes for the enzyme and accounts for approximately 80% of the type I cases. Type Ib GSD results from mutations in the SLC37A4 gene encoding the glucose-6-phosphate (G6P) transporter. Because the G-6-Pase enzyme is located on the inner membrane of the endoplasmic reticulum, the transporter is required for G6P to reach the enzyme. The conversion of G6P to glucose is the final common pathway of all endogenous glucose production; hence, GSD I is associated with the most severe fasting intolerance of the GSDs.

The G-6-Pase enzyme complex is located in the liver, kidney, and intestine. Accumulation of glycogen results in hepatomegaly and nephromegaly, and shunting of G6P into alternative pathways leads to hyperlactatemia, hyperuricemia, and hypertriglyceridemia.

**Glycogen Storage Disease Type Ia**

**Diagnosis**

Almost all people with GSD Ia have manifestations in the neonatal period. Lethargy, irritability, or tachypnea will often lead newborns to be evaluated by neonatologists, but the diagnosis is rarely made because the manifestations abate with initiation of frequent feeds. Children subsequently are often subclinical until 3 to 6 months of age when the interval between feeds is lengthened. GSD Ia is occasionally diagnosed during a routine physical examination after hepatomegaly and a protuberant abdomen are appreciated (Table 3). Usually, however, children are diagnosed when the aforementioned laboratory abnormalities are found during an evaluation for lethargy, seizures, respiratory distress, developmental delay, or failure to thrive. Rarely, people receive their diagnosis in adulthood, after evaluations for hyperlipidemia, gout, hepatomegaly, or hepatic tumors.

The simplest means of determining the probable defect in a child suspected of having a glycogenosis is to obtain critical blood measurements of glucose, lactate, and ketones during a fasting study (Table 4). A brief fasting study (3–4 hours) will result in hypoglycemia and hyperlactatemia. In contrast to the other hepatic forms of GSD, GSD I is hypoketotic (see Table 3). Genetic studies have become the recommended test for diagnosing GSD Ia. Assay of G6Pase activity on a liver biopsy should be reserved for those people in whom molecular analysis is nondiagnostic.

**Clinical management**

The aim of treatment is to prevent hypoglycemia and counter-regulation, thereby minimizing the secondary metabolic derangements and long-term complications. Dietary management may consist of continuous gastric tube feeds or uncooked cornstarch depending on several factors, including the age of the child and child and/or family preferences. Glucose concentrations should remain higher than 75 mg/dL to prevent counter-regulation; hyperglycemia (ie, glucose >100 mg/dL) should be avoided to minimize glycogen storage and decrease insulin production.
<table>
<thead>
<tr>
<th>GSD Type</th>
<th>Incidence</th>
<th>OMIM#</th>
<th>Enzyme or Protein Deficiency</th>
<th>Gene</th>
<th>Chromosome Location</th>
<th>Mode of Inheritance</th>
<th>High-Risk Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSD 0</td>
<td>Rare</td>
<td>240600</td>
<td>Glycogen synthase</td>
<td>GYS2</td>
<td>12p12.2</td>
<td>Autosomal Recessive</td>
<td>Italians</td>
</tr>
<tr>
<td>GSD Ia</td>
<td>1:100,000</td>
<td>232200</td>
<td>Glucose-6-phosphatase-α catalytic subunit</td>
<td>G6PC</td>
<td>17q21.31</td>
<td>Autosomal Recessive</td>
<td>Ashkenazi Jews, Mormons, Mexicans</td>
</tr>
<tr>
<td>GSD Ib</td>
<td>1:1,000,000</td>
<td>232220</td>
<td>Glucose-6-phosphate transporter</td>
<td>SLC37A4</td>
<td>11q23.3</td>
<td>Autosomal Recessive</td>
<td>Italian Native Americans</td>
</tr>
<tr>
<td>GSD III</td>
<td>1:100,000</td>
<td>232400</td>
<td>Glycogen debranching enzyme (includes 4-alpha-glucanotransferase and amylo-1,6-glucosidase activities)</td>
<td>AGL</td>
<td>1p21.2</td>
<td>Autosomal Recessive</td>
<td>Faroe Islanders, First Nation (Canada), North African Jews</td>
</tr>
<tr>
<td>GSD IV</td>
<td>1:600,000–1:800,000</td>
<td>232500</td>
<td>Glycogen-branching enzyme</td>
<td>GBE</td>
<td>3p12.3</td>
<td>Autosomal Recessive</td>
<td>—</td>
</tr>
<tr>
<td>GSD VI</td>
<td>1:100,000</td>
<td>232700</td>
<td>Glycogen phosphorylase (liver)</td>
<td>PYGL</td>
<td>14q22.1</td>
<td>Autosomal Recessive</td>
<td>Scottish</td>
</tr>
<tr>
<td>GSD IXa</td>
<td>306000</td>
<td>PHKA2</td>
<td>Xp22.13</td>
<td></td>
<td></td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>GSD IXb</td>
<td>261750</td>
<td>PHKB</td>
<td>16q12.1</td>
<td></td>
<td></td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>GSD IXc</td>
<td>613027</td>
<td>PHKG2</td>
<td>16p11.2</td>
<td></td>
<td></td>
<td></td>
<td>—</td>
</tr>
<tr>
<td>GSD XI</td>
<td>Rare</td>
<td>227810</td>
<td>GLUT2 transporter</td>
<td>SLC2A2</td>
<td>3q26.2</td>
<td>Autosomal Recessive</td>
<td>—</td>
</tr>
</tbody>
</table>
Due to intestinal immaturity and lack of amylase, cornstarch is rarely tolerated before 6 months of age. Low-dose cornstarch can be initiated between 6 to 12 months, but diarrhea may limit the efficacy of the treatment. Children younger than 2 years of age usually require feeds every 2 to 3.5 hours. Cornstarch feeds can usually be spaced to every 3 to 5 hours in older children and adults. The dose of cornstarch for children younger than 8 years of age can be estimated by calculating the basal glucose production rate using the following formula: $y = 0.0014x^3 - 0.214x^2 + 10.411x - 9.084$, in which $y = \text{mg/kg/min of glucose}$ and $x = \text{weight in kg}$. The brain is the major utilizer of glucose. Because the endogenous energy requirements for the brain are stable after 8 years of age, weight-based dosing is not recommended after this age, and a standard of 10 to 11 g of glucose per hour is used to estimate carbohydrate needs. Doses of cornstarch are individualized, based on glucose and lactate levels.

### Table 3
Clinical characteristic of the hepatic glycogen storage diseases

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristic Clinical Manifestations</th>
</tr>
</thead>
</table>
| Type 0    | • Normal liver size  
           | • Fasting ketotic hypoglycemia  
           | • Postprandial hyperglycemia without polyuria and polydipsia                                      |
| Type Ia   | • Hepatomegaly  
           | • Short stature and failure to thrive  
           | • Hypoglycemia  
           | • Hepatic adenomas  
           | • Renal calcification                                      |
| Type Ib   | • Same as Ia with additional consequences of neutrophil abnormalities (multiple and recurrent infections) |
           | • Severe iron-resistant anemia  
           | • Inflammatory bowel disease                                                           |
| Type III  | • Firm, very enlarged liver  
           | • Hypertrophic cardiomyopathy  
           | • Myopathy                                                                            |
| Type VI   | • Hepatomegaly  
           | • Ketotic hypoglycemia  
           | • Short stature                                                                         |
| Type IX   | • Hepatomegaly  
           | • Ketotic hypoglycemia (especially in boys)  
           | • Short stature  
           | • Attention-deficit hyperactivity disorder  
           | • Delayed puberty                                                        |

### Table 4
Biochemical characteristics of the hepatic glycogenoses

<table>
<thead>
<tr>
<th>Glycogen Storage Disease</th>
<th>Fasting Lactate</th>
<th>Postprandial Lactate</th>
<th>Fasting Ketones</th>
<th>Triglycerides</th>
<th>Uric Acid</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSD 0</td>
<td>Normal</td>
<td>++ +</td>
<td>+++</td>
<td>+/-</td>
<td>Normal</td>
<td>Low prealbumin</td>
</tr>
<tr>
<td>GSD I</td>
<td>++ +</td>
<td>Normal</td>
<td>Normal</td>
<td>+++</td>
<td>++</td>
<td>...</td>
</tr>
<tr>
<td>GSD III</td>
<td>Normal</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>Normal</td>
<td>Elevated CK (IIIa)</td>
</tr>
<tr>
<td>GSD VI</td>
<td>Normal</td>
<td>+/-</td>
<td>+++</td>
<td>+/-</td>
<td>Normal</td>
<td>Low prealbumin</td>
</tr>
<tr>
<td>GSD IX</td>
<td>Normal</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>Normal</td>
<td>Low prealbumin</td>
</tr>
</tbody>
</table>
monitoring, to maintain glucose concentrations higher than 75 mg/dL and lactate lower than 2.2 mmol/L. Cornstarch is mixed with water or a sugar-free liquid. Adding glucose is not recommended because it stimulates insulin production and offsets the advantage of the starch. An extended-release cornstarch formulation (Glycosade) is available for night feeds, and it has allowed older children and adults to have a 7 to 10 hour period of coverage without sacrificing metabolic control. In North America, Glycosade is not recommended for daytime coverage or for children younger than 5 years of age.

Restricted intake of galactose, sucrose, and fructose is recommended because these sugars will worsen the hepatomegaly and metabolic derangements. Multivitamin supplementation is required due to the restricted diet. Achieving glucose concentrations between 75 and 100 mg/dL is the key to maximizing metabolic control. In many GSD centers, people are hospitalized annually for titration of the therapy based on intensive glucose and lactate monitoring. Continuous glucose monitoring is used in some centers to identify periods of rapid change. Screening with annual abdominal ultrasounds and urine studies is recommended starting at 5 years of age. Most recommendations for treatment were generated through either the American College of Medical Genetics certified consensus guidelines or the European Study for GSD, which are both based on expert opinion.

### Disease complications
Complications commonly seen in people with poorly controlled disease are the following:

- Hepatic adenomas (HCAs): HCAs typically develop during puberty and malignant transformation can occur. During malignant transformation, traditional tumor markers can be normal. There is no difference in the rate of HCA formation in people treated with cornstarch when compared with continuous feeds. There is increasing evidence that higher lactate and triglyceride concentrations are associated with adenoma formation. Liver transplantation or surgical resection previously was performed when adenomas exceeded 5 cm. Liver transplantation has been associated with a high rate of secondary renal failure. Beegle and colleagues demonstrated regression of liver lesions if optimal metabolic control is achieved, and medical treatment is now recommended before surgery.

### Table 5
Overview of the disorders of gluconeogenesis

<table>
<thead>
<tr>
<th>Protein Deficiency</th>
<th>FBPase Deficiency</th>
<th>PC Deficiency</th>
<th>Cytosolic PEPCK Deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td>FBP1</td>
<td>PC</td>
<td>PCK1, PCK2</td>
</tr>
<tr>
<td>Incidence</td>
<td>1:350,000–900,000</td>
<td>1:250,000</td>
<td>Very rare</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Yes</td>
<td>Often</td>
<td>No, but liver failure in 1 report</td>
</tr>
<tr>
<td>CNS involvement</td>
<td>In case of fasting hypoglycemia</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>On fasting</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hyperlactatemia</td>
<td>On fasting</td>
<td>Depending on the feeding state and subtype of the disorder</td>
<td>Mild</td>
</tr>
</tbody>
</table>
• GSD nephropathy: Hyperfiltration begins early in life and the disease can progress with development of focal segmental glomerulosclerosis, interstitial fibrosis, and renal insufficiency. In 2002, the European Study for GSD reported that 100% of GSD Ia people developed microalbuminuria or proteinuria by 24 years of age. With improved care, the prevalence of GSD nephropathy has decreased and now few adults develop microalbuminuria or proteinuria.

• Osteoporosis: The cause of the abnormal bone mineralization is multifactorial, including insufficient calcium intake, vitamin D deficiency, hypercortisolemia, and hyperlactatemia. When optimal metabolic control is combined with appropriate calcium and vitamin D supplementation, normal bone densities are achieved.

• Renal calcification: This complication previously occurred in 70% of adults. Risk factors for renal calcification include hypercalciuria, elevated urinary uric acid concentrations, and hypocitraturia. Normalization of the urinary citrate has been successful at preventing nephrocalcinosis and nephrolithiasis.

• Other complications: Short stature, delayed puberty, and obesity previously were common in GSD Ia, but growth is now near normal. Pulmonary hypertension, polycystic ovarian disease, and a bleed diathesis rarely occur anymore.

**Prognosis**

Before the 1970s, most children with GSD I died in infancy or early childhood. Despite having severe hypoglycemia before diagnosis, most people with GSD Ia are neurologically normal because lactate can serve as an alternative fuel for the brain. With advances in medical and dietary management, the prognosis has markedly improved. Currently, children can develop into healthy adults, and more than 100 successful pregnancies have occurred in women with GSD Ia.

**Glycogen Storage Disease Type Ib**

**Diagnosis**

Early in life, people with GSD Ib may be clinically identical to those with GSD Ia. With aging, however, most people develop neutropenia, neutrophil dysfunction, and inflammatory bowel disease (IBD). As with all the GSDs, genetic studies are now the preferred method for diagnosing GSD Ib.

**Clinical management**

Achieving glucose concentrations between 75 and 100 mg/dL is the key to maximizing metabolic control. Gastrointestinal issues may appear early in life, and people frequently do not tolerate cornstarch therapy until 2 years of age. Glycosade has not been well tolerated in GSD Ib. Exacerbations of IBD may occur from the large cornstarch doses, and this has contributed to metabolic instability.

GSD Ib has the unique challenges of neutropenia and IBD. Recombinant human granulocyte-colony-stimulating factor (G-CSF) is used, but this population is prone to untoward effects (massive splenomegaly, splenic sequestration, splenic rupture, portal hypertension, and leukemia). Therefore, a starting dose of 0.5 to 2.5 μg/kg/d is recommended. Daily dosing has been found to result in fewer infections, and the dose should be adjusted based on symptoms and not the absolute neutrophil count. Supplementation with high-dose vitamin E may boost the neutrophil count, improve function, and allow less G-CSF therapy. Bone marrow studies are no longer deemed necessary before commencing the therapy.

Nonabsorbable salicylates (Pentasa, Asacol, and Lialda) are the first-line therapies for IBD. Steroids and immunomodulators must be used with caution because of the metabolic consequences and associated immune dysfunction.
Disease complications

- Neutropenia and recurrent infections: Neutropenia can appear at birth or with aging. It can be permanent or cyclical. Although the severity of neutrophil dysfunction is variable, recurrent bacterial infections (predominantly Staphylococcus aureus, Streptococcus pneumoniae, and Escherichia coli) are common without treatment. Clostridium difficile infections are common, and this pathogen should be considered whenever chronic diarrhea is present. Most deaths in the past were due to severe infections; therefore, G-CSF is used by most centers. Recent studies suggest that the bone marrow function may be normal in GSD Ib and that the neutropenia is caused by apoptosis of the white blood cells.

- IBD: IBD has been diagnosed as early as 13 months of age, and most people become symptomatic between 5 and 8 years of age. Poor growth and an iron-resistant anemia often are present before abdominal symptomatology. Screening for IBD is performed with a combination of laboratory studies, including assessment of inflammatory makers (sedimentation rate or C-reactive protein), stool calprotectin, and IBD serologic studies. Stool calprotectin requires functioning neutrophils and, therefore, may result in a false-negative result. The disease is usually localized to the small intestine, and a normal colonoscopy does not rule out the complication. Capsule endoscopies can be used to look for evidence of IBD, but some people are treated empirically if they present with the constellation of growth failure, systemic inflammation, anemia, and abdominal symptoms. G-CSF helps decrease the symptoms; however, it is not sufficient by itself to treat the condition.

- Mouth ulcers and periodontal disease: Mouth ulcers and periodontal disease are common likely due to the combination of neutropenia and IBD. Aggressive dental hygiene is recommended with dental visits every 3 to 6 months. Topical therapy with chlorhexidine may help decrease the severity of the mouth ulcers and gum inflammation; however, plaque formation with the medication can be problematic.

Prognosis

Long-term complications in GSD Ib seem to be less frequent than in GSD Ia. Life-threatening infections can occur, but they are uncommon in people who are treated with G-CSF. IBD is the primary cause of morbidity in this population. Many adults with GSD Ib are clinically doing well, and numerous children have been born to mothers with GSD Ib.

Glycogen Storage Disease Type III (Cori or Forbes Disease)

GSD III is caused by deficiency of glycogen debrancher enzyme. The terminal chains of glycogen can be broken down normally; glycogenolysis, however, is arrested when the outermost branch points are reached. As a result of the defect, abnormal glycogen (limit dextrin) accumulates in affected tissues. Type IIIa accounts for 85% of people with GSD III, and involves the liver, heart, and muscles; type IIIb only affects the liver. Both GSD IIIa and IIIb are caused by mutations in the AGL gene.

Diagnosis

GSD III has a wide clinical spectrum. Hepatic involvement leads to hepatomegaly and fasting hypoglycemia, which may be indistinguishable in infancy from GSD I. People with GSD III can synthesize glucose via GNG, and energy formation from fatty acid oxidation is intact. As a result, the hypoglycemia often is not as severe as in GSD I, and is typically associated with prominent ketosis. Muscle involvement leads to a
chronic myopathy, muscle weakness, and pain, but these manifestations do not present in childhood.\textsuperscript{47}

Although fasting hypoglycemia can occur, most people present after failure to thrive, hepatomegaly, or abnormal hepatic transaminases are incidentally found (see Table 3). GSD III is often mistaken for a viral hepatitis, and aspartate aminotransferase and alanine aminotransferase concentrations may exceed 1000 U/L. Other common laboratory abnormalities include elevation of creatine kinase (CK), a low pre-albumin concentration, and hyperlipidemia. Abnormalities in the muscle enzymes, however, may not be present until children are ambulating.

GSD III can be differentiated from GSD I biochemically by the presence of ketones, lack of fasting hyperlactatemia or nephromegaly, and involvement of the muscles in type IIIa. Genetic studies are the preferred method for diagnosing GSD III. Liver biopsies are no longer recommended if GSD III is suspected. If a biopsy is performed, glycogen-filled hepatocytes with portal fibrosis are characteristic, and abnormal glycogen structure can be identified on electron microscopy. Measurement of enzyme activity in skin fibroblasts or lymphocytes can be used if available.

\textbf{Clinical management}

Treatment is based on avoidance of carbohydrate storage, minimizing ketosis, and preventing muscle damage. Protein can be used both as a substrate for endogenous glucose production and as a fuel for the muscles.\textsuperscript{48} Treatment with at least 3 g/kg/d of protein is recommended, and doses are adjusted to normalize prealbumin, total protein, and CK concentrations. Low-dose uncooked cornstarch or continuous feeds are also used to achieve glucose concentrations higher than 75 mg/dL and beta-hydroxybutyrate concentrations lower than 0.3 mmol/L. Glycosade has been used successfully when overnight hypoglycemia or ketosis occurs on traditional therapy.\textsuperscript{49} Even though fructose, sucrose, and galactose can be used, total carbohydrate intake is restricted to avoid excessive glycogen storage and to minimize insulin secretion. Because cardiac disease can occur at any age, annual echocardiograms are recommended, and abdominal ultrasounds are obtained every 1 to 2 years to screen for liver disease.\textsuperscript{46}

\textbf{Disease complications}

- Failure to thrive: Poor growth is common in early childhood due to a combination of chronic ketosis and protein deficiency. With optimal treatment, growth normalizes.
- Hypertrophic cardiomyopathy: Cardiac hypertrophy can present in the first year of life, but concentric left ventricular hypertrophy most commonly presents in childhood or adolescence. Most people have asymptomatic hypertrophy with relatively normal ventricular function, but severe and potentially lethal cardiac dysfunction, obstruction, and arrhythmias can occur. There are numerous articles documenting reversal of the associated hypertrophic cardiomyopathy using dietary interventions that restrict carbohydrates.\textsuperscript{50,51}
- Myopathy: Hypotonia is common at diagnosis, and asymptomatic CK elevation develops in childhood. Decreased stamina and muscle pain often occur in adolescence, and slowly progressive proximal muscle weakness can develop in adulthood. The myopathy is the primary source of morbidity in this population.
- Liver disease: Liver symptoms predominate in childhood, but long-term complications are uncommon. HCAs occur in less than 10% of adults.\textsuperscript{52} Hepatic fibrosis is common, but cirrhosis and portal hypertension infrequently occur if
treatment is maximized and alcohol is avoided. Hepatocellular carcinoma is a rare complication in GSD III.\(^{53}\)

- Type 2 diabetes mellitus: There may be an increased risk for developing type 2 diabetes mellitus. Restriction of carbohydrate intake and regular exercise should be the first measures to manage this complication.

**Prognosis**

The prognosis for people with GSD III is very good. Complications are rare in childhood if excessive sugar and carbohydrate intake are avoided. Recent studies have demonstrated slowing or prevention of muscle symptoms with a high protein diet, limited intake of carbohydrates, and avoidance of near maximal anaerobic activities.\(^{47}\)

**Glycogen Storage Disease Type VI (Hers Disease) and Glycogen Storage Disease Type IX**

Types VI and IX GSDs are considered together because both disorders result in abnormal hepatic phosphorylase activity. GSD VI is caused by a deficiency of liver glycogen phosphorylase.\(^{54}\) GSD IX is caused by deficiency in glycogen phosphorylase kinase. The phosphorylase kinase enzyme is composed of 4 subunits that are encoded by different genes: alpha, beta, gamma, and delta subunits. The alpha subunit is encoded on the X-chromosome and accounts for the classic condition.\(^{55}\) Because phosphorylase kinase is required to activate glycogen phosphorylase, GSD VI and IX show significant phenotypic overlap. There is evidence that GSD IX is the most common form of GSD.\(^{56}\)

**Diagnosis**

People usually present in infancy or early childhood with growth retardation, hypotonia, and prominent hepatomegaly. Ketotic hypoglycemia, or even ketotic normoglycemia, can occur.\(^{57}\) However, the hypoglycemia is often unrecognized because the ketones blunt neuroglycopenic symptoms. Hypotonia may lead to delayed motor development. Cognitive and/or speech delays have been reported. Rarely, children present during the school-age years when hepatomegaly is appreciated during an evaluation for attention deficit disorder, hyperlipidemia, short stature, or delayed puberty.\(^{58}\)

It is possible to diagnose phosphorylase deficiency by assaying the activity of the enzyme in leukocytes and erythrocytes. The blood assay, however, lacks sensitivity because there are tissue-specific isoforms of this enzyme. Biopsies are not required to make the diagnosis, but glycogen-filled hepatocytes with noninflammatory fibrosis are seen. Genetic studies are the preferred method for diagnosing GSDs VI and IX.

**Clinical management**

Treatment is based on avoidance of carbohydrate storage and minimizing ketosis. A high protein diet (2–2.5 g/kg/d) is used because amino acids can serve as a substrate for GNG. Doses are adjusted to normalize prealbumin concentrations. Although most people with GSD IX can make it through the night with cornstarch and protein, cornstarch feeds in the middle of the night are sometimes required to prevent hypoglycemia and ketosis. For these people, Glycosade can be considered.\(^{49}\) Carbohydrate restriction is recommended to avoid glycogen storage and to minimize insulin secretion. Due to the risk of liver scarring, annual abdominal ultrasounds are recommended.

**Disease complications**

- Short stature: Poor growth is common when inadequate protein supplementation or chronic ketosis is present.
- Cirrhosis: People with markedly elevated hepatic transaminases are at higher risk of hepatic fibrosis and cirrhosis.
**Prognosis**

GSD VI and IX have an outstanding prognosis. It is clear that treatment improves growth, stamina, and prevents complications.\(^5^9\) Mutations in the gamma subunit, however, may be associated with a more severe phenotype.\(^6^0\) A small percentage of people with mutations in the alpha subunit are also at risk for cirrhosis.\(^6^1\) Mutations in the beta subunit are usually associated with mild disease.

**Glycogen Storage Disease Type 0**

GSD 0 is caused by a deficiency of the hepatic isoform of glycogen synthase, leading to a marked decrease in liver glycogen content.\(^6^2\) After consumption of carbohydrate, the inability to store glucose as glycogen in the liver results in postprandial hyperglycemia and hyperlactatemia. Fasting can cause severe ketotic hypoglycemia.\(^6^3\)

**Diagnosis**

Most children are identified incidentally when ketotic hypoglycemia is documented during a gastrointestinal illness. Postprandial hyperglycemia and fasting ketonuria can be confused as early diabetes, and GSD 0 should be considered in any child with asymptomatic hyperglycemia or glucosuria.\(^6^4\) There is significant clinical variability, and it can present with seizures, growth failure, or hypoglycemia.\(^6^5\)

GSD 0 can be diagnosed biochemically. Following consumption of a glucose load or mixed meal, postprandial hyperglycemia and hyperlactatemia occur. Fasting results in ketotic hypoglycemia. Liver biopsies are not recommended, and sequencing of GYS2 is used to confirm the diagnosis.

**Clinical management**

The goal of treatment is to prevent hypoglycemia and ketosis. Protein supplementation is recommended, and cornstarch is usually administered 2 to 4 times per day. Blood glucose, lactate, and ketone monitoring are used to determine the cornstarch doses. Protein supplementation is based on symptoms and prealbumin concentrations. Sugar and carbohydrate intake are restricted to avoid hyperglycemia and hyperlactatemia.

**Disease complications**

Long-term complications are extremely rare in GSD 0. Consumption of sugars leads to hyperglycemia, which can cause elevation of the hemoglobin A1c. Osteoporosis can occur from decreased bone mineralization in the setting of chronic ketosis. Neither liver nor renal disease has been described.

**Prognosis**

The prognosis for people with GSD 0 is outstanding. Treatment, however, normalizes growth and improves stamina.

**INHERITED DISORDERS OF GLUCONEOGENESIS**

The formation of glucose from non–hexose metabolic precursors (mainly lactate, pyruvate, glycerol, and alanine) is called GNG. The conversion of pyruvate into glucose is the central pathway for GNG reactions. The glycolysis and GNG pathways are almost identical, but 3 nonreversible enzymatic reactions characterize the disorders of GNG:

1. Glucose-6-phosphate (G6P) is hydrolyzed by glucose-6-phosphatase. The associated inherited disorder is GSD I.
2. Fructose 1,6-bisphosphate is hydrolyzed by FBPase. The associated inherited GNG disorder is FBPase deficiency.
3. Conversion of pyruvate to phosphoenolpyruvate is affected in 2 stages:
   a. Pyruvate must first be carboxylated into oxaloacetate; the associated disorder
      is the mitochondrial matrix enzyme PC deficiency. In this disorder, there is a
      combined defect of GNG and the Krebs cycle.
   b. Because oxaloacetate cannot diffuse freely out of the mitochondrion, it is
      translocated into the cytoplasm via the malate/aspartate shuttle. Synthesis of
      phosphoenolpyruvate from oxaloacetate is catalyzed by cytoplasmic phospho-
      enolpyruvate carboxykinase (PEPCK).

   The biochemical phenotype of GNG disorders is characterized by fasting intoler-
   ance with associated recurrent hypoglycemia with lactic acidosis with or without
   ketosis (Table 5).

**Fructose-1,6-Bisphosphatase Deficiency**

FBPase catalyzes hydrolysis of fructose 1,6-bisphosphate into fructose 6-phosphate.

**Diagnosis**

FBPase deficiency is associated with relatively mild fasting hypoglycemia, severe
lactic acidosis, and moderate hepatomegaly during crises. The crucial role of
FBPase in the perinatal transition of glucose homeostasis is reflected in that about
half of the affected people present as hypoglycemic newborns with severe meta-
bolic acidosis–associated hyperventilation. The remaining people usually present
during catabolic periods with ketotic hypoglycemia and hyperlactatemia, hyperala-
ninemia, hyperketonemia, increased lactate to pyruvate ratio, elevated plasma uric
acid concentration, glyceroluria, and pseudohypertriglyceridemia. Lactate concen-
trations during acute episodes may accumulate up to 25 mmol/L, causing acidosis
and necessitating bicarbonate infusions. Upstream to the primary metabolic block,
the impaired cytosolic-free NAD to NADH ratio shifts the equilibrium between py-
ruvate and lactate, which explains the increasing lactate to pyruvate ratio (<40).
The diagnosis can be made noninvasively by molecular analysis of the FBP1
gene.

**Clinical management**

Endogenous carbohydrate requirements are relatively high in newborns and young
infants when hepatic glycogen stores are relatively small. Children may be pre-
scribed a late-evening meal with uncooked cornstarch or continuous nocturnal
gastric drip feeding. During illness, oral management with glucose polymers is
started at home to prevent progressive metabolic derangement. In these conditions,
people should not be given fructose or sucrose because the rapidly formed but
slowly metabolized fructose-1-phosphate inhibits liver glycogen phosphorylase.
People need an emergency protocol ensuring timely intravenous glucose manage-
ment to correct hypoglycemia. Relatively high infusion rates are needed (10%
dextrose at 1.25–1.5 times maintenance) to reverse metabolic derangement and
end a metabolic crisis.

**Disease complications**

Complications are rare except for acute metabolic crises. The condition may be fatal
during the neonatal period due to severe hypoglycemia and acidosis. Consumption of
glycerol and sorbitol can precipitate a metabolic crisis.

**Prognosis**

The prognosis is good with proper dietary management.

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Weinstein et al
**Pyruvate Carboxylase Deficiency**

The chemical reaction of the biotinylated mitochondrial matrix enzyme PC is carboxylation of pyruvate into oxaloacetate. The enzyme is expressed at high levels in liver and kidney. PC is essential for anaplerosis of the Krebs cycle by replenishment of intramitochondrial oxaloacetate. PC also exports acetyl CoA out of mitochondria via the pyruvate-malate shuttle, which is important for lipogenesis.

**Diagnosis**

PC deficiency presents with failure to thrive, developmental delay, and recurrent seizures. An evaluation reveals hypoglycemia, metabolic acidosis, hyperammonemia, or ketosis. In neonates, a high lactate to pyruvate ratio with a low hydroxybutyrate to acetoacetate ratio is suggestive of the diagnosis. Cystic periventricular leukomalacia associated with lactic acidosis can also be seen. After carbohydrate intake, blood lactate concentrations decrease. PC deficiency is categorized into 3 overlapping phenotypes that probably represent a continuum:

- Type A: infantile or North American form
- Type B: severe neonatal or French form
- Type C: intermittent or benign form.

The serum and urine amino acid profile may reveal hyperalaninemia, low aspartic acid, and increased concentrations of citrulline and lysine. Measurement of PC activity in cultured skin fibroblasts and sequence analysis of the PC gene confirm the diagnosis.

**Clinical management**

Management aims to prevent catabolism, to correct anaplerosis, and to enhance residual enzyme activity. Treatments include intravenous 10% dextrose infusion; bicarbonate; dietary management; and supplementation of citrate, aspartate, triheptanoin, dichloroacetate, biotin, and thiamine. The ketogenic diet is strictly contraindicated.

**Disease complications**

Neurologic defects and development delay are the primary complications in PC. Cystic lesions and gliosis in the cortex, basal ganglia, brain stem, and cerebellum can develop. There can be ventricular dilation, cortical and white matter atrophy, and periventricular white matter cysts. Hypomyelination can also occur with type A PC deficiency. There is no consensus regarding the best treatment approach or when to go to liver transplant.

**Prognosis**

The outcome is poor for severe cases with types A and B PC deficiency. In the most severe cases, neurologic damage already starts prenatally. People with minimal residual PC activity usually do not survive the neonatal period.

**Phosphoenolpyruvate Carboxykinase Deficiency**

The chemical reaction of PEPCK catalyzes the conversion of oxaloacetate into phosphoenolpyruvate and carbon dioxide. PEPCK deficiency is an extremely rare condition. The first reports on 4 cases with PEPCK deficiency originate from the 1970s and were followed by few publications in the following decades. Interpretation of the clinical relevance of PEPCK deficiency has been difficult because the diagnosis has relied solely on enzymatic testing, which was unreliable. Owing to the lack of confirmed cases and rarity of cases, there is a paucity of literature on the natural history and clinical manifestations of PEPCK deficiency.
REFERENCES


