Inborn Errors of Metabolism with Hypoglycemia

Glycogen Storage Diseases and Inherited Disorders of Gluconeogenesis

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KEYWORDS

• Glycogen storage disease • Hypoglycemia • Ketosis • Lactate
• Disorders of gluconeogenesis • Ketotic hypoglycemia

KEY POINTS

- The mechanisms that maintain blood glucose are complex and controlled by hormones, glycogenolysis, gluconeogenesis, mitochondrial fatty acid oxidation, and ketogenesis.
- Glycogen storage diseases (GSDs) comprise several inherited diseases caused by abnormalities of the enzymes and transporters in glycogen synthesis and degradation.
- Hypoglycemia is the primary manifestation of the hepatic GSDs (types 0, I, III, VI, IX, and XI).
- Complications in the hepatic GSDs can be prevented or delayed if near optimal metabolic control is attained.
- Disorders of gluconeogenesis are typically characterized by fasting intolerance with associated recurrent hypoglycemia with lactic acidosis with or without ketosis.

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

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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 α-1,4-linkages that elongate into chains of glucose molecules. A branching enzyme leads to formation of α-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 1
Metabolic and endocrine causes of hypoglycemia

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