Glycogen Storage Disease Type I: Prognostic Factors and Treatment

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Abstract

Glycogen storage disease type I (GSD I) is an inherited disorder that hinders the ability of the liver to effectively break down stored glycogen, leading to difficulties in maintaining appropriate blood sugar levels. The main treatment for this aspect of GSD I involves the use of filgrastim, although patients often require additional treatment for recurrent infections, and an enlarged spleen is a common side effect. Acute lactic acidosis, which can cause respiratory distress and ketoacidosis in newborns, can be triggered by minor illnesses and accompanied by severe hypoglycemia. Early diagnosis and prompt initiation of appropriate metabolic treatment are crucial in preventing the devastating effects of this condition. The overall prognosis and long-term efficacy of treatment are influenced by various factors, including the timing of diagnosis, adherence to dietary protocols, and availability of appropriate medical interventions.

Introduction

Glycogen storage disease type I (GSD I) is an inherited disorder that hinders the ability of the liver to effectively break down stored glycogen, leading to difficulties in maintaining appropriate blood sugar levels. GSD I can be classified into two main types, GSD Ia and GSD Ib, each characterized by distinct causes, symptoms, and treatments. There may also be rarer subtypes known as GSD Ic and GSD Id, which involve translocases for inorganic phosphate or glucose, respectively. However, recent research suggests that the methods used to differentiate GSD Ic and GSD Id from GSD Ib lack reliability and, therefore, classify them as GSD Ib[7].

GSD Ia arises from a deficiency of the enzyme glucose-6-phosphatase, whereas GSD Ib results from a deficiency in the transport protein glucose-6-phosphate translocase. As glycogenolysis is the primary metabolic process through which the liver supplies glucose to the body during fasting, deficiencies in these enzymes can lead to severe hypoglycemia and excessive glycogen accumulation in the liver and kidneys over time[3]. Owing to the buildup of glycogen, individuals with GSD I typically exhibit enlarged livers associated with non-alcoholic fatty liver disease. Initially, other liver and kidney functions remained intact in GSD I; however, they became susceptible to additional complications[6]. Without proper treatment, GSD I can cause chronic low blood sugar, which may result in high lactic acid levels, abnormal lipid levels in the

blood, and other health issues.

The primary treatment for all forms of GSD I involves frequent feeding of corn starch or other carbohydrates. GSD Ib also manifests as chronic neutropenia, which occurs due to dysfunction in neutrophil production in the bone marrow. This immunodeficiency, if left untreated, renders individuals with GSD Ib vulnerable to infections. The main treatment for this aspect of GSD Ib involves the use of filgrastim, although patients often require additional treatment for recurrent infections, and an enlarged spleen is a common side effect. GSD Ib patients often present with inflammatory bowel disease as well[9]. GSD I is the most prevalent among the various glycogen storage disease, with an incidence of approximately 1 in 100,000 births in the general American population and approximately 1 in 20,000 births among Ashkenazi Jews. The disease was named after German physician Edgar von Gierke, who initially described it in 1929[8].

Hypogycemia

The primary clinical symptom shared by GSD Ia and Ib is low blood sugar (hypoglycemia), which often serves as the initial indication for diagnosing the disease. During fetal development, the transfer of maternal glucose across the placenta prevents hypoglycemia. However, after birth, the inability to maintain adequate blood glucose levels from stored glycogen in the liver leads to measurable hypoglycemia within 1-2 hours of feeding[1]. Without proper dietary intervention, prolonged hypoglycemia can result in sudden lactic acidosis, which can cause respiratory distress and ketoacidosis in newborns.

The neurological manifestations of hypoglycemia tend to be less severe in GSD I than in other cases. Instead of experiencing acute hypoglycemia, individuals with GSD I experience persistent mild hypoglycemia[1]. The reduced likelihood of neurological symptoms is attributed to adaptation of the brain to mild hypoglycemia. With lower blood glucose levels, the brain adjusts and utilizes alternative fuels such as lactate. These gradual metabolic adaptations during infancy cause severe symptoms, such as unconsciousness or seizures, that are uncommon prior to diagnosis[10]. During the early weeks of life, infants with undiagnosed GSD I can tolerate persistent hypoglycemia and compensate for lactic acidosis between feedings, without displaying symptoms[5]. However, without consistent carbohydrate intake, blood glucose levels typically range between 25 and 50 mg/dL (1.4 2.8 mmol/L). After several weeks or months without proper treatment involving regular oral carbohydrates, infants will start showing signs of hypoglycemia and lactic acidosis. These symptoms may include paleness, clamminess, irritability, respiratory distress, and inability to sleep through the night, even in the second year of life. While developmental delay is not an inherent effect of GSDI, it is common if the condition is not diagnosed in early infancy[5].

Symptoms

Initial research on GSD has mistakenly identified numerous clinical manifestations as the primary features of genetic disorders[5]. However, further investigations have revealed that these clinical features are actually consequences of only one or two fundamental abnormalities: impaired liver function in converting stored glycogen into glucose through glycogenolysis, leading to a deficiency in fasting blood glucose levels. The impaired ability of neutrophils to uptake glucose results in neutrophil dysfunction and neutropenia[5].

These fundamental abnormalities give rise to a limited number of primary clinical manifestations that are crucial in diagnosing GSD I, including hypoglycemia (low blood sugar) caused by inadequate breakdown of glycogen (glycogenolysis). An enlarged liver is associated with nonalcoholic fatty liver disease due to glycogen accumulation. Increased susceptibility to infections in GSD Ib is due to neutropenia and neutrophil dysfunction[7]. Affected individuals often exhibit secondary clinical manifestations that are linked to one or more of the following primary clinical features: elevated levels of uric acid in the blood, posing a risk of gout or kidney damage caused by prolonged hypoglycemia, and low serum insulin levels. High levels of lactic acid in the blood can lead to lactic acidosis in severe cases, resulting from prolonged hypoglycemia[5].

Development of hepatic adenomas in adulthood and an associated risk of anemia, potentially due to blood glucose dysregulation in the presence of non-alcoholic fatty liver disease[5]. Inflammatory bowel disease along with an increased risk of anemia, is caused by neutrophil dysfunction and is aggravated by the higher carbohydrate intake required to prevent hypoglycemia. Furthermore, the treatment of primary clinical manifestations often leads to additional clinical manifestations such as enlarged pancreas (pancreatic hypertrophy) due to increased carbohydrate intake, which triggers frequent insulin responses[5]. Splenomegaly (enlarged spleen) results from long-term use of filgrastim to treat neutropenia, leading to the sequestration of blood factors in the spleen. Potentially decreased platelet count in the blood in GSD Ib due to the long-term use of filgrastim leads to the sequestration of platelets in the spleen. Anemia in GSD Ib results from the long-term use of filgrastim, causing the sequestration of hemoglobin in the spleen, potentially worsened by uncontrolled inflammatory bowel disease[7].

Genetics

GSDI is inherited in an autosomal recessive pattern, meaning that individuals need to inherit two copies of the faulty gene to develop the disease. Individuals who carry only one copy of the faulty gene are unaffected and do not exhibit symptoms. Similar to other autosomal recessive disorders, when two carriers of the disease have a child, there is a 25% chance that the child will inherit both copies of the faulty gene and show signs of disease[1]. Parents who do not have GSD I but have a child with the

condition can be presumed carriers.

Prenatal diagnosis has been performed through fetal liver biopsy at 18-22 weeks of gestation, although there is currently no proposed fetal treatment. Prenatal diagnosis can also be achieved by analyzing fetal DNA obtained through chorionic villus sampling, when the fetus is known to be at risk. The most common forms of GSD I are referred to as GSD Ia and GSD Ib, with GSD Ia accounting for more than 80% of the diagnosed cases and GSD Ib accounting for less than 20%. Few rare forms have been identified. GSDIa occurs due to mutations in the G6PC gene, which encodes the glucose-6-phosphatase enzyme.

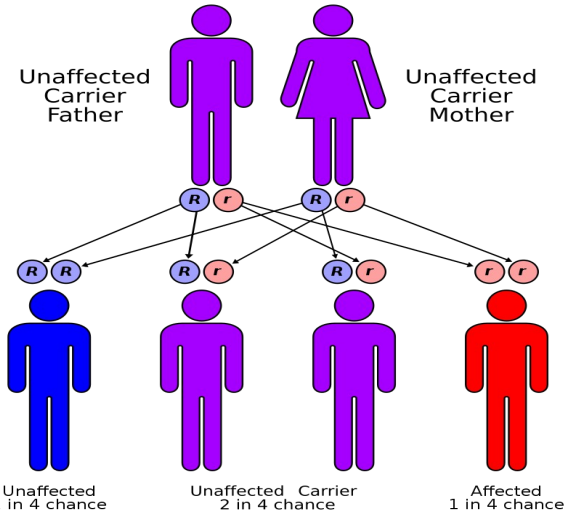

Figure 1

This gene is located on the chromosome 17q21. GSD Ib occurs as a result of mutations in SLC37A4, also known as "G6PT1," which encodes the glucose-6-phosphate transporter. GSD Ic is caused by mutations in the SLC17A3 and SLC37A4 genes. Glucose-6-phosphatase is an enzyme found in the inner membrane of the endoplasmic reticulum (ER). It consists of a catalytic unit associated with a calcium-binding protein and three transport proteins (T1, T2, T3) that facilitate the movement of glucose-6-phosphate (G6P), phosphate, and glucose (respectively) into and out of the enzyme, respectively[8].

Pathophysiology

Glycogen stored in the liver and kidneys serves as a readily available source of glucose to maintain the blood glucose levels between meals. After consuming a meal containing carbohydrates, insulin levels increase, leading liver cells to take up glucose from the bloodstream. Glucose is then converted to glucose-6-phosphate (G6P) by the enzyme glucokinase. Liver cells add these G6P molecules to glycogen chains, a process known as glycogen synthesis. Excess G6P is also used to produce triglycerides, which are exported and stored as fat in the adipose tissue. Once the

digestion of a meal is complete, insulin levels decrease and liver cells begin to break down glucose molecules from glycogen in the form of G6P. This process is known as glycogenolysis.

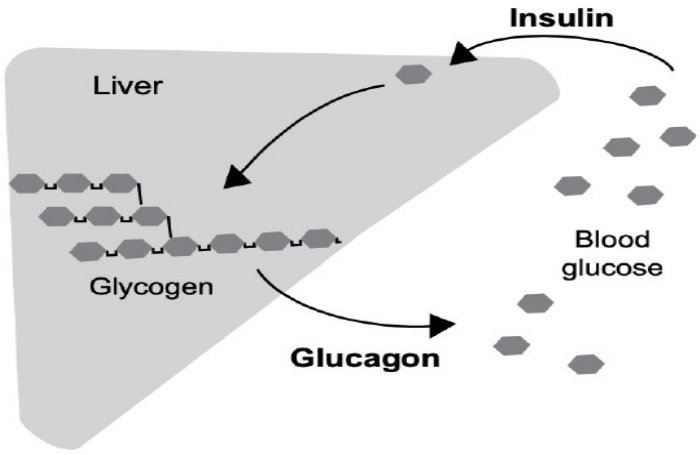

Figure 2

G6P remains within the liver cells unless it is dephosphorylated by glucose-6-phosphatase. This dephosphorylation reaction results in the release of free glucose and phosphate ions (PO4). Free glucose molecules can then be transported out of liver cells into the bloodstream to provide an adequate supply of glucose to the brain and other organs. Glycogenolysis can meet the glucose requirements of the adult body for approximately 12-18 hours. During prolonged fasting, as insulin levels continue to decrease, muscle proteins and triglycerides from adipose tissue break down. This process generates amino acids (mainly alanine), free fatty acids, and lactic acid[10]. Free fatty acids are converted to ketones and acetyl-CoA. Amino acids and lactic acid are utilized in liver cells to synthesize G6P through a process called gluconeogenesis. The final step of gluconeogenesis, similar to the last step of glycogenolysis, involves dephosphorylation of G6P by glucose-6-phosphatase, resulting in the release of free glucose and phosphate ions (PO4). Therefore, glucose-6-phosphatase plays a crucial role in the final steps of both glycogenolysis and gluconeogenesis during fasting[1].

This impact is amplified because the high levels of glucose-6-phosphate inhibit earlier key steps in both processes. The deficiency of glucose-6-phosphatase leads to several metabolic effects, including hypoglycemia, lactic acidosis, hypertriglyceridemia, and hyperuricemia. In GSD I, hypoglycemia occurs during fasting, typically approximately 4 h after meal completion. The inability to maintain sufficient blood glucose levels during fasting is due to impairments in both glycogenolysis and gluconeogenesis. Fasting hypoglycemia is often the most significant issue in GSD I and is frequently the reason for diagnosis. Chronic hypoglycemia results in secondary metabolic adaptations such as persistently low insulin levels and elevated levels of glucagon and cortisol.

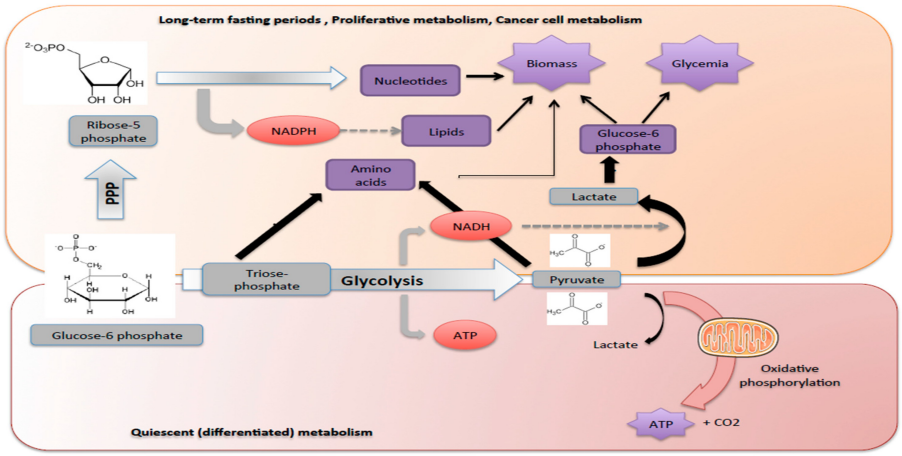

Figure 3

Lactic acidosis is caused by the impairment of gluconeogenesis. Lactic acid is produced in both the liver and muscles, and is converted to pyruvic acid through oxidation by NAD+. Pyruvic acid is then converted to G6P through the gluconeogenic pathway[13]. However, the accumulation of G6P inhibits the conversion of lactate to pyruvate. During fasting, lactic acid levels increase as glucose levels decrease, and in individuals with GSD I, lactic acid levels may not return to normal even when glucose levels are restored. Hypertriglyceridemia, characterized by increased triglyceride levels, is another indirect effect of impaired gluconeogenesis. This was further amplified by chronically low insulin levels. During fasting, triglycerides are normally broken down into free fatty acids and ketones[5].

Increased levels of lactate and lactic acidosis

Individuals with GSD I exhibit elevated levels of lactic acid in their bloodstream owing to impaired gluconeogenesis. Baseline elevations generally range from 4 to 10 mol/mL, which does not have clinical implications. However, during and after episodes of low blood sugar, lactate levels abruptly rose above 15 mol/mL, which is the threshold for lactic acidosis[5]. The symptoms of lactic acidosis include vomiting and hyperpnea, both of which can worsen hypoglycemia in individuals with GSD I. Emergency medical care is required to stabilize blood oxygen levels and restore blood glucose levels during acute lactic acidosis[10].

Identifying lactic acidosis in undiagnosed children can be challenging, as initial symptoms often resemble common childhood infections such as gastroenteritis or pneumonia, both of which can exacerbate severe hypoglycemia in undiagnosed children. Persistent elevation of lactate levels leads to increased levels of uric acid, ketoacids, and free fatty acids, further raising the anion gap[1]. In both adults and children, high lactate concentrations can cause significant muscular discomfort. This discomfort is an intensified version of the burning sensation felt by runners in their

quadriceps after sprinting, which is caused by a temporary build-up of lactic acid. Proper management of hypoglycemia in GSD I prevents lactic acidosis.

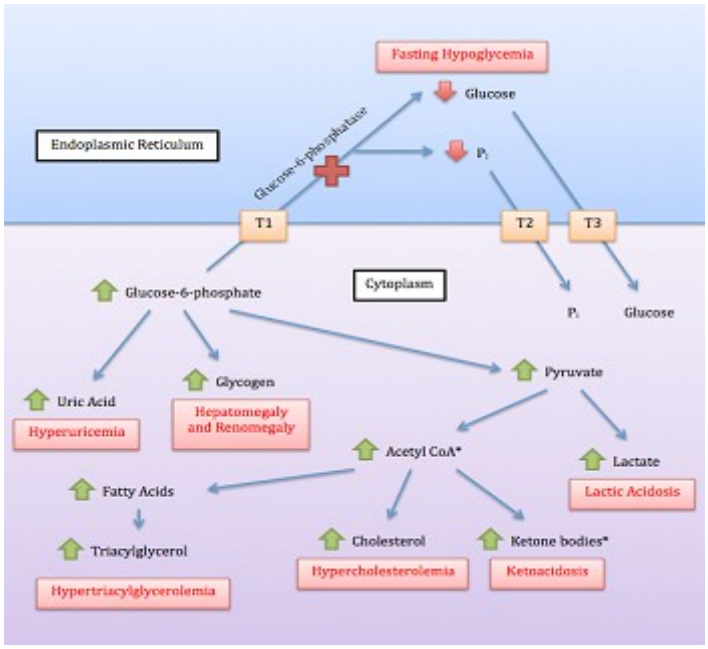

Figure 4

Elevated uric acid level and associated complications

Elevated levels of uric acid are often accompanied by elevated lactic acid levels in individuals with GSD I. Increased levels of blood-borne lactic acid compete with urate for the same transport mechanism in the kidney tubules, limiting the rate at which uric acid can be eliminated through the urine[12]. Additionally, increased purine catabolism may have contributed to this effect. Unmanaged GSD I can result in uric acid levels ranging from 6 to 12 mg/dl (530–1060 umol/L). In some cases, allopurinol is necessary to lower blood urate levels. Hyperuricemia in GSD I patients can lead to the development of kidney stones and accumulation of uric acid crystals in joints, causing kidney disease and gout, respectively1[13].

Hyperlipidemia and its effects on the plasma

Elevated triglyceride levels in GSD I are a consequence of low serum insulin levels during prolonged hypoglycemia episodes. The intracellular accumulation of glucose-6-phosphate with secondary shunting to pyruvate, which is converted to acetyl-CoA, also contributes to this effect[8]. Acetyl-CoA is transported to the cytosol, where fatty acid and cholesterol synthesis occurs. Triglyceride levels above the range of 3.4 mmol/L (300 mg/dL) can result in visible lipemia and, in some cases, mild pseudohyponatremia due to a reduced aqueous fraction of blood plasma. Cholesterol levels in GSD I patients are typically only mildly elevated compared to other lipid levels[9].

Diagnosis

Several different issues can lead to a diagnosis, usually occurring before the age of two: seizures or other symptoms indicating severe fasting hypoglycemia. Enlarged liver causing abdominal protrusion. Hyperventilation and apparent respiratory distress caused by metabolic acidosis. Episodes of vomiting resulting from metabolic acidosis are often triggered by minor illnesses and accompanied by hypoglycemia. Once a diagnosis is suspected, the presence of multiple clinical and laboratory features strongly suggests this condition. If hepatomegaly, fasting hypoglycemia, poor growth, lactic acidosis, hyperuricemia, hypertriglyceridemia, and enlarged kidneys detected through ultrasound are present, GSD I is the most likely diagnosis[2].

Other possible conditions on the differential diagnosis list include glycogenose types III and VI, fructose 1,6-bisphosphatase deficiency, and a few other conditions. However, none of these features is likely to exhibit all the features observed in GSD I. The next step usually involved a carefully monitored fasting period. Hypoglycemia often occurs within six hours[10]. A critical blood sample taken during hypoglycemia typically shows mild metabolic acidosis, elevated levels of free fatty acids and beta-hydroxybutyrate, very low insulin levels, and high levels of glucagon, cortisol, and growth hormones. The administration of intramuscular or intravenous glucagon (0.25 to 1 mg, depending on age) or epinephrine results in a slight increase in blood sugar. The diagnosis was definitively confirmed through liver biopsy with electron microscopy and the measurement of glucose-6-phosphatase activity in the tissue. Specific gene testing, which has become available in recent years, can also be used for confirmation[11].

Treatments

The main objective of treatment is to prevent hypoglycemia and manage secondary metabolic abnormalities by providing frequent meals high in glucose or starch, which are easily converted into glucose. Since the liver is unable to adequately supply sugar, the total carbohydrate intake should approximate the 24-hour glucose production rate. The recommended diet consists of approximately 65-70% carbohydrate, 10-15% protein, and 20-25% fat[13]. It is important to supply at least one-third of the carbohydrates during the night, ensuring that a young child does not go for more than 3-4 hours without carbohydrate intake. Maintaining adequate blood glucose levels is the primary focus of GSD I treatment, which aims to keep blood glucose above the cutoff for hypoglycemia, typically 72 mg/dL (4.0 mmol/L)[11].

Patients with GSD Ib require additional attention to manage their neutropenia. Proper blood glucose management is crucial for preventing the severe effects of elevated lactic acid and uric acid levels in the blood, as well as the development of hepatic

adenomas. In the past three decades, two methods have been used to achieve this goal in young children: (1) continuous nocturnal gastric infusion of glucose or starch and (2) nighttime feeding of uncooked cornstarch[2]. Continuous infusion of an elemental formula, glucose polymer, and/or cornstarch can be administered overnight using a nasogastric or gastrostomy tube and pump. However, there have been cases of sudden death due to malfunction or disconnection; therefore, periodic cornstarch feeding has become the preferred method. Cornstarch is an inexpensive method for gradual digestion of glucose. One tablet contained nearly 9 g of carbohydrates (36 calories). Although it requires parents to wake up every 3-4 hours to administer cornstarch, it is a safer and more cost-effective option that does not require specialized equipment. A typical requirement for a young child is 1.6 g/kg every 4 h[12].

Long-term management aims to eliminate hypoglycemic symptoms, maintain normal growth, and achieve normal levels of glucose, lactic acid, and electrolytes, with only mild elevations in uric acid and triglycerides. It is important to minimize the intake of carbohydrates that must be converted to glucose-6-phosphate (G6P) for utilization, such as galactose and fructose. While elemental formulas are available for infants, many foods contain fructose or galactose in the form of sucrose or lactose, making adherence to dietary restrictions challenging after infancy. For patients with persistent elevation of uric acid levels above 6.5 mg/dL, allopurinol treatment is recommended to prevent uric acid deposition in the kidneys and joints[13].

Due to the potential for impaired platelet function, coagulation ability should be assessed and the metabolic state normalized before surgery. Bleeding time may be improved with 1-2 days of glucose loading and ddavp[4]. During surgery, the intravenous fluids should contain 10% dextrose and no lactate. Liver transplantation has been performed in some patients with GSD type 1b, resulting in the resolution of hypoglycemic episodes and the need to avoid natural sources of sugar. However, it does not resolve chronic neutropenia or risk of infection[3]. In cases of episodes of acute metabolic acidosis triggered by minor illnesses, prompt medical attention is necessary. If vomiting persists for more than 2-4 hours, the child should be evaluated for dehydration, acidosis, and hypoglycemia. Intravenous fluids should be provided at a rate above the maintenance rate.

Prognosis

In the absence of proper metabolic treatment, individuals with GSD I have fatal consequences, such as severe hypoglycemia and acidosis, leading to death during infancy or childhood. Survivors experience growth impairment and delayed puberty because of chronically low insulin levels. Intellectual disability resulting from recurrent and severe hypoglycemia can be prevented with appropriate treatment. Liver complications have proven to be a significant concern in some patients[1].

In the second decade of life or later, liver adenomas can develop, and there is a low

risk of malignant transformation into hepatoma or hepatic carcinomas, which can be detected through alpha-fetoprotein screening. In cases where advanced hepatic complications have arisen, some children show improvement after liver transplantation[7]. Adolescents and adults with GSD I have reported additional problems including hyperuricemic gout, pancreatitis, and chronic kidney failure. However, atherosclerotic complications are uncommon, despite the presence of hyperlipidemia. With early diagnosis to prevent serious harm, timely reversal of acidotic episodes, and appropriate long-term treatment, most children maintain good health. While there are exceptions and certain considerations, adults with GSD I can enjoy relatively good health and lifespan. However, owing to the lack of effective treatment options before the mid-1980s, information on long-term efficacy is limited[10].

Conclusion

In conclusion, Glycogen Storage Disease Type I (GSD I) is a complex metabolic disorder characterized by impaired glucose metabolism and the inability to properly store glycogen in the liver and muscles. The consequences of GSD I can be severe, leading to life-threatening hypoglycemia, metabolic acidosis, and various complications affecting multiple organ systems. Early diagnosis and prompt initiation of appropriate metabolic treatment are crucial in preventing the devastating effects of GSD I. Frequent feedings of foods high in glucose or starch, along with careful monitoring of carbohydrate intake, play a central role in maintaining stable blood glucose levels and preventing metabolic derangements.

Continuous nocturnal gastric infusion or night-time feedings of uncooked cornstarch have proven effective strategies in managing glucose levels during sleep. The long-term management of GSD I aims to eliminate hypoglycemic symptoms, maintain normal growth, and control metabolic parameters such as glucose, lactic acid, and electrolyte levels. Additionally, attention must be given to managing complications associated with GSD I, such as hyperuricemia, liver adenomas, and kidney-related issues. Advancements in liver transplantation have offered hope for patients with advanced hepatic complications, leading to improved outcomes in some cases. However, the overall prognosis and long-term efficacy of treatment are influenced by various factors, including the timing of diagnosis, adherence to dietary protocols, and availability of appropriate medical interventions. While significant progress has been made in understanding and managing GSD I, further research is needed to enhance diagnostic methods, refine treatment strategies, and explore potential therapies to address the diverse challenges faced by individuals with this condition.

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