REVIEW

Dietary Management of the Glycogen Storage Diseases: Evolution of Treatment and Ongoing Controversies

Katalin M Ross,[1] Iris A Ferrecchia,[1] Kathryn R Dahlberg,[1] Monika Dambska,[1] Patrick T Ryan,[1] and David A Weinstein[1,2]

[1] *Glycogen Storage Disease Program, Connecticut Children's, Hartford, CT, USA; and* [2] *Department of Pediatrics, University of Connecticut School of Medicine, Farmington, CT, USA*

ABSTRACT

The hepatic glycogen storage diseases (GSDs) are a group of disorders where abnormal storage or release of glycogen leads to potentially life-threatening hypoglycemia and metabolic disturbances. Dietary interventions have markedly improved the outcome for these disorders, from a previously fatal condition to one where people can do well with proper care. This article chronicles the evolution of dietary management and treatment of the hepatic GSDs (types 0, I, III, VI, IX, and XI). We examine historic and current approaches for preventing hypoglycemia associated with GSDs. There is a lack of consensus on the optimal dietary management of GSDs despite decades of research, and the ongoing controversies are discussed. *Adv Nutr* 2019;00:1–8.

Keywords: glycogen storage disease, ketosis, lactate, hypoglycemia, dietary management, uncooked cornstarch, protein, treatment, Glycosade

Introduction

The hepatic glycogen storage diseases (GSDs) are a group of inborn errors of metabolism caused by abnormalities of the enzymes that catalyze the synthesis or degradation of glycogen. The first GSD was described by Edgar von Gierke in 1929 (1) and there are now at least 16 recognized types (**Table 1**).

Hypoglycemia is characteristic of all hepatic GSDs due to aberrant conversion of glycogen to glucose. The treatment, however, varies depending on the metabolic pathway involved. There are 3 major types of hepatic GSDs:

1) GSDs with defective glycogenolysis and gluconeogenesis (types Ia and Ib)
2) GSDs with defective glycogenolysis but intact gluconeogenesis (types III, VI, and IX)
3) GSDs with altered storage of glycogen (types 0, IV, and XI).

Type I GSD results from impaired glucose-6-phosphatase activity and is the most severe of the liver forms of GSD from a euglycemic vantage point because the conversion of glucose-6-phosphate to glucose is the final step for both glycogenolysis and gluconeogenesis. Types 0, III, VI, and IX are ketotic forms of GSD, and they present with less severe hypoglycemia because lactate, amino acids, and glycerol (from fatty acid oxidation) can serve as precursors for gluconeogenesis. Type 0 GSD has abnormal synthesis of glycogen, and type XI GSD is due to a defect in glucose transport across the GLUT-2 glucose channel in the liver, pancreas, kidneys, and intestines. Although GSD type IV is also a hepatic form of GSD (branching enzyme activity), it will not be discussed here because there is a paucity of literature and evidenced-based recommendations on the role and efficacy of nutritional therapy for this disorder, which is often treated with a liver transplant. Given the variety of pathophysiology, the treatment recommendations are vastly different based on the underlying enzyme defect. However, nutritional therapy is the mainstay of treatment across the types of GSDs, and understanding the pathophysiology allows better understanding of the role of nutrition in their treatment.

Support for this article was provided by philanthropic assistance obtained from the Global Center for Glycogen Storage Disease.
Author disclosures: IAF and PTR, no conflicts of interest. KMR, KRD, MD, and DAW all receive grant support related to the Glyde study from Vitaflo, Inc.
Address correspondence to KMR (e-mail: kross@connecticutchildrens.org).

Background

Nutritional therapy has remained the primary treatment for GSDs over the past 50 y, and this article seeks to

TABLE 1 Glycogen storage disease genetic and enzymatic overview[1]

Type	Affected gene	Chromosome location	Year disease described
Type 0	*GYS2* (glycogen synthase)	Chromosome 12 (12p12.1)	1963
Type Ia (von Gierke disease)	*G6PC* (glucose-6-phosphatase)	Chromosome 17 (17q21.31)	1929
Type Ib	*G6PT1 (SLC37A4)* (glucose-6-phosphate transporter)	Chromosome 11 (11q23.3)	1978
Type II (Pompe disease)	*GAA* (glucosidase alpha, acid)	Chromosome 17 (17q25.3)	1932
Type IIIa (Forbes or Cori disease)	*AGL* (glycogen debranching enzyme)	Chromosome 1 (1p21.2)	1928
Type IIIb	*AGL* (glycogen debranching enzyme; liver only)	Chromosome 1 (1p21.2)	1928
Type IV (Anderson disease)	*GBE* (glycogen branching enzyme)	Chromosome 3 (3p12.2)	1956
Type V (McArdle disease)	*PYGM* (muscle glycogen phosphorylase)	Chromosome 11 (11q13.1)	1951
Type VI (Hers disease)	*PYGL* (liver glycogen phosphorylase)	Chromosome 14 (14q22.1)	1959
Type VII (Tarui disease)	*PFKM* (muscle phosphofructokinase)	Chromosome 12 (12q13.11)	1965
Type IXa	*PHKA2* (phosphorylase kinase alpha 2)	Chromosome X (Xp22.13)	1969
Type IXb	*PHKB* (phosphorylase kinase beta)	Chromosome 16 (16p12.1)	1981
Type IXc	*PHKG2* (phosphorylase kinase, gamma 2)	Chromosome 16 (16p11.2)	1982
Type IXd	*PHKA1* (phosphorylase kinase, alpha 1)	Chromosome X (Xq13.1)	1986
Type X	*PGAM2* (phosphoglycerate mutase, muscle)	Chromosome 7 (7p13)	1993
Type XI (Fanconi–Bickel syndrome)	*SLC2A2* (GLUT-2 glucose transporter)	Chromosome 3 (3q26.2)	1949
Type XII	*ALDOA* (aldolase A)	Chromosome 16 (16p11.2)	1973
Type XIII	*ENO3* (β-enolase)	Chromosome 17 (17p13.2)	2001
Type XIV	*PGM1* (phosphoglucomutase 1)	Chromosome 1 (1p31.3)	2009
Type XV (glycogenin deficiency)	*GYG1* (glycogenin 1)	Chromosome 3 (3q24)	2010

[1]Gene names and chromosome locations obtained from Online Mendelian Inheritance in Man (OMIM) website (2).

review the evolution of modern therapy for GSDs. The primary goals of management of all the hepatic GSDs are to prevent hypoglycemia and minimize acidosis. Glucose homeostasis is finely regulated by a complex integration of hormones (e.g. glucagon, growth hormone, epinephrine, and cortisol) and metabolic pathways (e.g., glycogenolysis, gluconeogenesis, and fatty acid oxidation). Counterregulation commences when glucose concentrations are <70 mg/dL. In GSD type I, shunting of glucose-6-phosphate into the alternative pathways leads to accumulation of lactate, triglycerides, and uric acid. In the ketotic forms of GSD, ketoacids (particularly β-hydroxybutyrate) predominate in the other forms of GSD due to increased fatty acid oxidation.

Evolution of GSD Treatment

The first clue regarding the nutritional therapy for GSD dates back to 1939 when a case study was published in which a child with hypoglycemia and hepatomegaly demonstrated no rise in blood glucose after oral or intravenous delivery of galactose. Blood lactate concentrations, however, were elevated enough to cause respiratory distress from metabolic acidosis (3). In 1956, Schwartz et al. (4) demonstrated that ingestion of fructose produced high lactate concentrations and associated acidosis, as did galactose to a lesser degree. As a result, some practitioners began restricting sugars that required hepatic metabolism. A treatment was proposed with a mixture of evaporated milk and water supplemented with maltose and casein (a milk protein); however, there was no guidance regarding how dosing of the formula should be determined (4).

Portacaval shunts

In the 1960s, portacaval shunts were introduced as a way to maintain blood glucose concentrations in the systemic circulation (5–7). Portacaval shunting involved major surgery and connected the hepatic portal vein to the inferior vena cava diverting blood flow away from the liver. This shunting resulted in 75% of dietary carbohydrates bypassing the liver. This, in turn, limited glycogen storage, and preserved dietary carbohydrate for use as an energy source for the brain and body. Following this procedure, high-carbohydrate diets were encouraged. Although this intervention allowed prolonged intervals between feeds, nocturnal hypoglycemia continued to occur (8). GSD continued to be almost universally fatal until continuous glucose therapy was introduced in 1972.

Continuous feeds

In 1972, dextrose, a component of total parenteral nutrition (TPN), was found to ameliorate all metabolic abnormalities associated with type I GSD. Within 4 wk of initiation of TPN, patients experienced euglycemia, reduction in hepatomegaly, and improved biochemical markers of metabolic control (9). Subsequent studies demonstrated that high glucose intake exceeding the estimated glucose requirements using dietary carbohydrate intake also resulted in reduced lactate and triglyceride concentrations (10). Burr et al. (11) concluded that intragastric feeding was as efficacious as both parenteral nutrition and portacaval shunting without the added risk of invasive intervention. They also concluded that shunting of substrate and/or hormones from the liver, as in portacaval shunt and parenteral nutrition, is not essential for reversing the anomalies associated with GSD, but rather continuous

nutrition per se would achieve the same ends (11). Medical management with high-glucose intragastric continuous feeding around the clock, or a regimen with nocturnal drip feeds combined with starchy meals every 3 h during the day, was proposed in lieu of surgery (10). Continuous intragastric feeds, however, were associated with severe hypoglycemia if the feed was interrupted, and children suffered from frequent episodes of hypoglycemia, seizures, and even death due to pump failures.

Although it became apparent that higher doses of carbohydrates were required to mitigate the laboratory abnormalities, quantification of the precise needs did not occur until 1976, when Bier et al. (12) published the results of isotope studies demonstrating the threshold for glycogenolysis. Glucose requirements were found not to be linear with age or weight, but rather correlated with brain size. The following mathematical equation was created, which is still used today to estimate glucose requirements in children aged ≤8 y:

$$Y = 0.0014X^3 - 0.214X^2 + 10.411\,X - 9.084,$$

where Y = milligrams glucose per minute and X = body weight in kilograms.

The formula had several limitations, however, and it deviated from the demonstrated isotope estimates when weight exceeded 30 kg. The formula was also found to underestimate requirements during puberty, and adults were found to require less glucose per kilogram per minute than young growing children (13).

Cornstarch

In the 1970s, investigations centered on finding slow-release carbohydrate sources that could maintain glucose concentrations for more than 3 h. Numerous starches and carbohydrates were tested, and cornstarch was found to be the most effective alternative therapy (14). Cornstarch had several advantages over other starches and continuous feeds. First, it resulted in lower insulin concentrations compared with continuous feeds (15). As a result, lower amounts of cornstarch could be used, and glucose doses equivalent to 5.3–7.6 mg/kg/min could maintain euglycemia whereas continuous feedings required 8–10 mg/kg/min to maintain normal glucose concentrations. Intermittent cornstarch dosing was also found to decrease glycogen storage (15).

Cornstarch also has the advantage of being neuroprotective when hypoglycemia occurs. Pump failure or leakage occurring in a high-insulin state causes rapidly falling glucose concentrations. In addition, insulin suppresses formation of alternative fuels (i.e., ketones and lactate), and thus seizures are common from pump interruptions. In contrast, cornstarch has a slower rate of fall, and the lower insulin concentrations allow lactate to accumulate in GSD type I, which helps to protect against seizures or neurological damage. In GSD types 0, III, VI, IX, and XI when glucose levels decrease, ketones are created from fatty acid oxidation, and the ketones can serve as an alternative fuel. Although other forms of starch absorb faster or slower than cornstarch, the latter has the advantage of most closely matching the basal metabolic needs thus avoiding excessive glycogen storage or hypoglycemia.

Although cornstarch remains the mainstay in maintaining euglycemia in GSD, dosing has changed over the years. When introduced, 2 primary treatment strategies were used: large doses given 2 times per day or 1.75 g/kg given every 6 h. Although these strategies allowed survival to occur, patients continued to struggle with poor metabolic control (16). Adding dextrose to cornstarch was attempted, but this accentuated insulin production and led to greater instability (17). Critics of cornstarch raised concerns about the ability of patients and/or family members to adhere to this demanding schedule, the palatability, and the lack of nutritional completeness of cornstarch (18). Complications, such as gut dysbiosis, low intestinal pH, and inflammation, have also been suggested by some investigators to be due to the therapy itself (19). With time, it became apparent that smaller doses administered more frequently resulted in increased euglycemia, decreased hypoglycemia, and improved metabolic control. With cornstarch administered every 3–4 h around the clock and proper nutrition, normal biochemical markers of metabolic control can be achieved (20).

Despite concerns about the nutritional deficiencies resulting from dietary restrictions and dependence upon nonfood products (cornstarch) (21), frequent daytime treatment with uncooked cornstarch became widely accepted in the 1990s, beginning at age 6–12 mo. Younger infants lack sufficient production of pancreatic amylase to digest uncooked cornstarch. Oral glucose delivery in infants aged <6 mo was recommended every 1.5–2.5 h (22, 23), whereas oral cornstarch delivery for older children was recommended at 5–6 feedings per day (24).

Extended-release cornstarch (Glycosade)

Treatment with traditional cornstarch improved the markers of metabolic control for patients with GSD of all types. The median duration between cornstarch doses was 4.25 h, which required at least 1 feeding in the middle of the night (20). Starch with a slower rate of absorption was needed to extend sleep periods for people with GSD. The efficacy of a new waxy maize starch (Glycosade) was demonstrated in overnight trials in patients with GSD I (25). The new product effectively lengthened the time of euglycemia between nocturnal feedings and added safety through avoidance of an overnight feed. Sleep and quality of life also improved by omission of the middle-of-the-night feeding (26). The extended-release waxy maize has been approved in countries worldwide since 2009. In the United States, the extended-release preparation has been approved for nocturnal use in GSD patients who are aged ≥5 y. All patients with GSD 0, III, VI, and IX tolerated the waxy maize starch; however, the majority of patients with GSD Ib, who are prone to inflammatory bowel disease, discontinued use of the starch due to increased abdominal pain, flatulence, and diarrhea. Additionally, the strong taste of corn and its

granular texture were cited as reasons for discontinuing use of the waxy maize starch across the types (27, 28).

Controversies in GSD I management

GSD I is caused by deficiency of glucose-6-phosphatase (GSD Ia) or the glucose-6-phosphate transporter (GSD Ib). The main symptoms are hypoglycemia, hyperlactatemia, hypertriglyceridemia, hyperuricemia, hepatomegaly, and short stature. Inflammatory bowel disease and immunodeficiency are specific for GSD Ib. Although there has been substantial progress in the care of people with GSD I, there continue to be controversies surrounding the appropriate dietary approach to managing this disorder. Seven of the primary controversies are discussed: *1*) appropriate dietary restrictions; *2*) dosing of dietary carbohydrates; *3*) daily cornstarch dosing; *4*) use of the extended-release waxy maize starch; *5*) use of continuous feeds; *6*) ketogenic diet in GSD I; and *7*) supplementation in GSD I.

Dietary restrictions.

Researchers have known since the 1950s that dietary sucrose, fructose, and galactose in GSD I result in elevated lactate concentrations and acidosis (4, 29), yet there is no consensus on the amount of these nonutilizable sugars to restrict (30). No formal study, however, has been performed to determine the precise threshold where fructose and galactose cause biochemical abnormalities in GSD I. Through an institutional review board–approved natural history study and >20 y of clinical and research experience, our center has found that limiting the amount of nonutilizable sugars to <2.5 g/meal is essential to optimize metabolic control. In addition to all fruits, which contain a high amount of fructose, it is recommended that patients restrict other foods (vegetables, dairy) that contain high concentrations of natural sugars. Alcohol must also be restricted due to liver inflammation and aberrant alcohol metabolism. All sugary drinks should also be avoided. It is important to note that artificial sweeteners can also impact metabolic control. In particular, sorbitol is converted to fructose during digestion, whereas other sugar alcohols (i.e., maltitol) can have a laxative effect.

Use of continuous feeds.

Beginning in the 1970s, continuous gastric feeds were attempted to treat GSD until cornstarch was attempted (10). Although continuous feeds were effective, extraneous problems such as pump failures, tube dislodgements, and tube leaks still led to undertreatment, or even catastrophic failures leading to patient deaths. Despite decades of discussion, no consensus on the use of continuous nighttime feeds versus intermittent cornstarch dosing around the clock has been achieved (18, 31). Some recommend that the decision be left to patient preference (18), whereas other clinicians point out that due to the high insulin state resulting from continuous feeds, it is more advantageous to use a starch preparation (27).

Cornstarch dosing.

In many centers, cornstarch is dosed by volume (i.e., tablespoons or scoops) instead of by weight. Although commonly performed, dosing in this manner leads to a lack of precision, and the recent guidelines prefer weighing cornstarch by weight on a gram scale instead of by volume (32). In GSD I, it is best to mix the cornstarch with water or a sugar-free beverage until completely dissolved and then immediately consume. The container used for mixing the cornstarch should be rinsed and the rinsing consumed to ensure that the prescribed amount is taken. Cornstarch should also be stored in a sealed container at room temperature and should be consumed within 1 mo of opening.

Regular titration and evaluation of metabolic control is essential in both children and adults to accommodate changing metabolic needs. Times of increased metabolic demand, such as puberty, physical activity, and acute illness, need to be compensated for either with snacks or by adjustment of cornstarch dosing in order to maintain proper metabolic control. Further study is needed in adult patients to determine the effects of aging on cornstarch dosing and its effect on metabolic control.

Whereas the initial publications reported cornstarch dosing every 6 h, more recent studies have demonstrated improved metabolic control with cornstarch dosing every 3–5 h (20). Increasing the dose amount does not prolong the duration of its action for >5 h, and increased counterregulation occurs when the interval dosing of cornstarch is spaced beyond this threshold resulting in higher triglyceride and lactate concentrations. Because of this limited dosing interval, there was a need for longer-term solutions, leading to the development of waxy maize extended-release cornstarch.

Use of waxy maize extended-release cornstarch.

There is no consensus regarding the age when the extended-release preparation should be used. In many countries it is approved for use at ≥2 y, but in the United States the extended-release formulation is limited to patients aged ≥5 y (27, 28). However, even in the United States, some centers are using it for an off-label indication at an earlier age. There has been no study published to date that demonstrates safety and efficacy in the younger cohort. A short-term pilot study illustrated no difference between cornstarch and Glycosade in the length of time that euglycemia could be maintained in children aged 3 and 4 y (33). Possible reasons for this difference are gastrointestinal tolerance of the waxy maize starch and rapid growth.

Although the extended-release preparation has now been used for >8 y, dosing guidelines have not been published. Some patients are unable to tolerate the volume required to maintain euglycemia through the night, and taste, texture, cost, and insurance coverage are continuing problems. Due to inflammatory bowel disease and problems with gastrointestinal intolerance, caution is advised in the use of the waxy maize starch in GSD type Ib (27). To date,

there are few data demonstrating efficacy of the extended-release preparation during the daytime period (27, 34), but an international investigation assessing daytime use of the extended-release formulation is presently underway (clinicaltrials.gov NCT02318966). Because energy demands during the day are greater than at night, the slow-release waxy maize starch might not be digested fast enough to meet the daytime needs.

Dietary carbohydrates.

Historically, there was no limit to the amount of dietary carbohydrates consumed in GSD I. Carbohydrates were given to maintain euglycemia. It is now understood that if the combined energy of the carbohydrate from cornstarch and from food exceeds energy used, glycogen will be stored, leading to hepatomegaly. Importantly, excessive carbohydrate intake also results in hyperinsulinemia, which can cause rebound hypoglycemia. GSD patients who consume more energy than they need will be overweight, and they can experience a glycemic "rollercoaster," which can exacerbate hyperlipidemia, elevate hepatic transaminases, and cause general metabolic instability. As such, it is recommended that patients consume complex carbohydrates instead of simple carbohydrates. Although no formal studies have been published, our center recommends no more than 15 g of total carbohydrates to be consumed at each meal and only 5 g carbohydrates prescribed at each snack.

Ketogenic diet in GSD I.

Ketogenic diets are now commonly used in many metabolic disorders (35). Consuming a low-to-no-carbohydrate diet results in breakdown of fat as an energy source producing ketones as a by-product. Although limited carbohydrate intake is recommended in GSD type I, ketogenic diets have been associated with poor outcomes. It is important to note that GSD I is a hypoketotic disorder, presumably due to malonyl CoA–induced suppression of lipolysis (36, 37). Use in the GSD Ia population has been associated with severe hypoglycemia, neurological injury, and strokes due to the combination of hypoglycemia and low alternative fuels (D Weinstein unpublished data, 2019).

Supplementation in GSD I.

Due to the deficiencies in important nutrients and vitamins that such dietary restrictions incur, it is recommended that all GSD I patients take regular sugar-free multivitamin and calcium supplements. Vitamin D supplementation is often recommended to prevent osteoporosis, which has heretofore been a sequela of GSD I (38, 39). Daily vitamin E supplementation is also recommended in GSD Ib to support neutrophil formation and function (40). Additional supplementation can be required on an individual basis, in consultation with the patient's physician.

Ketotic forms of GSD (types 0, III, VI, IX, and XI)

GSD III, also known as Cori disease or Forbes disease, is a defect in the debrancher enzyme and presents with hepatomegaly, ketotic hypoglycemia, impaired growth, myopathy, and neurological concerns. Over time, in the absence of strict adherence to dietary regimens, there is a propensity to develop cirrhosis and hypertrophic cardiomyopathy (41, 42). GSD VI, also known as Hers disease, and GSD IX result from disruptions in phosphorylase activity. Prolonged fasting or illness often results in ketosis and mild hypoglycemia because gluconeogenesis is still intact (43). Type IX GSD was once considered a benign condition due to its mild presentation; however, there is a wide range of clinical severity (44). It generally presents early in childhood, with hepatomegaly and growth failure. Hepatic fibrosis and cirrhosis can occur but can regress with optimal treatment (39).

In the ketotic GSDs (III, VI, IX), a consistent exogenous supply of glucose and protein serves as an alternative fuel in gluconeogenesis. Infants can require more frequent daytime feedings and nighttime continuous feeds. Historically, the diet in GSD III, VI, and IX focused on remediating hypoglycemia with carbohydrates, and simple sugars were not restricted. Replacing some carbohydrates with protein improved growth and reversed myopathy (41). The GSD III consensus guidelines published by the American College of Medical Genetics recommend approximately 3–4 g protein/kg/d (42). Cornstarch is also used, but dosing must be precise. Undertreatment results in ketone formation, whereas overtreatment contributes to excessive glycogen storage and cardiomyopathy (43). In younger children, ketosis inhibits growth, and chronic acidosis contributes to development of osteoporosis. Lack of sufficient dietary protein can manifest in exercise intolerance, muscle fatigue, and muscle cramps (45). Alcohol must be strictly avoided because it inhibits gluconeogenesis and can lead to severe hypoglycemia and seizures.

GSD 0 is associated with hypoglycemia that tends to be milder than in other GSD types (46). Short stature, failure to thrive, and laboratory abnormalities also occur. Postprandial lactic acidosis and fasting ketosis are characteristics of the disease. The liver is of normal size. Treatment consists of cornstarch, protein supplementation, and limiting of dietary carbohydrates. Patients with GSD 0 should also be supplemented with calcium and vitamin D due to the risk of osteoporosis (46).

GSD XI (Fanconi–Bickel syndrome) was first described in 1949. This disorder classically presents with short stature, hypoglycemia, hepatomegaly, hypophosphatemia rickets, postprandial hyperglycemia, and proximal renal tubular dysfunction (47). Treatment for GSD type XI consists of dietary modifications that include removal of glucose and galactose. Small amounts of fructose are allowed (47) to correct acute hypoglycemia. To prolong euglycemia between meals, uncooked cornstarch is recommended in small doses around the clock. Supplementation with vitamin D, phosphate, and bicarbonate is often required (47, 48).

Controversies in GSDs with defective glycogenolysis but intact gluconeogenesis (types III, VI, and IX) and GSDs with altered glycogen storage (types 0 and XI) include: *1*) protein requirements, *2*) carbohydrate requirements, and *3*) use of ketogenic diet.

Protein requirements.
Understanding the role of a protein-enriched diet has evolved over the years. Fernandes and Huijing (49), as early as 1968, advocated for frequent small feeds high in protein for GSD III. Ten years later, Leonard et al. (50) described a diet with twice the normal intake of protein for age to prevent secondary metabolic abnormalities. Even the use of continuous high-protein enteral therapy has been proposed (42, 51). The GSD III consensus guidelines recommend 3–4 g protein/kg of body weight. The effect of diet on blood glucose should be monitored and adjusted individually. Protein supplementation is titrated to ameliorate muscle symptoms, lower creatine kinase concentrations, and normalize nutritional markers (total protein and prealbumin). Critics of high protein intake have raised concerns about the impact of protein on renal function, but Okechuku et al. (52) showed that there were no significant renal complications related to high protein intake in the ketotic forms of GSD. The recommendation for protein for types 0, VI, and IX is 2–3 g protein/kg body weight/d (53) and for GSD type XI is 2–2.5 g protein/kg/d (48). Protein serves as an alternative energy source that reduces glycogen storage and increases prealbumin concentrations (48).

Carbohydrate requirements.
Dagli and Weinstein (43) recognized the possibility of carbohydrate overtreatment in ketotic GSDs. The consensus guidelines for GSD III (42) recommended that infants and children be treated with cornstarch to remediate hypoglycemia; however, much less cornstarch is required than for GSD type I (32). For types VI and IX carbohydrates should be ~45–50% of the daily intake. Basal metabolic needs change with aging, and carbohydrate and protein protocols should be adjusted with age (12). Monitoring of blood glucose and ketones is essential to determine the optimal balance of protein and cornstarch at any stage of development. For GSD types 0 and XI there is a lack of literature recommending the specific amounts of carbohydrates.

Ketogenic diet.
Several publications have emphasized positive outcomes of high-protein or even ketogenic diets in management of ketotic GSD types 0, III, IV, VI, IX, and XI (39, 54, 55). The reversal of cardiomyopathy, and improvement of hepatomegaly and myopathy have been reported with a ketogenic diet (54). No article to date has defined the optimal β-hydroxybutyrate concentration should a ketogenic diet be used. High ketone concentrations can also worsen hepatic transaminase elevation, delay growth, and contribute to osteoporosis.

Conclusions

Diet and nutrition have turned GSD from a once fatal disorder to one with an outstanding prognosis (56). Diet, not medications, remains the primary treatment. Due to the rarity of the GSDs, a multicenter collaboration would be helpful in studying a larger group of patients across cultural backgrounds. Sharing treatment regimens that produce efficacious outcomes will improve the quality of life and increase the body of knowledge for children and adults who live with these rare diseases.

Acknowledgments

We acknowledge and thank Ilan Small, Corbinian Wanner, Malaya Mount, and Amber Barry for their contributions and assistance with proofreading and editing the article. The authors' responsibilities were as follows—KMR, IAF, KRD, MD, PTR, DAW: wrote sections and coordinated manuscript writing; and all authors: contributed to the concept, and reviewed, read, and approved the final manuscript.

References

1. von Gierke E. Hepato-nephromegalia glykogenica (Glykogenspeicherkrankheit der Leber und Nieren). Beitr Path Anat 1929;82:497–513.
2. Online Mendelian Inheritance in Man (OMIM) [Internet]. Baltimore, MD: McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), August 2019. Available from: https://omim.org.
3. Himwich HE, Baker Z, Fazekas JF. Respiratory metabolism of infant brain. Am J Physiol 1939;125:601–6.
4. Schwartz R, Ashmore J, Renold AE. Galactose tolerance in glycogen storage disease. Pediatr 1957;19:585–95.
5. Sexton AW, Marchioro TL, Waddell WR. Liver deglycogenation after portacaval transposition. Surg Forum 1964;15:120–2.
6. Starzl TE, Marchioro TL, Sexton AW, Illingworth B, Waddel WR, Faris TD, Herrmann TJ. The effect of portacaval transposition on carbohydrate metabolism: experimental and clinical observations. Surgery 1965;57:687–97.
7. Riddell AG, Davies RP, Clark AD. Portacaval transposition in the treatment of glycogen storage disease. Lancet 1966;2:1146.
8. Starzl TE, Brown BI, Blanchard H, Brettschneider L. Portal diversion in glycogen storage disease. Surgery 1969;65(3):504–6.
9. Folkman J, Philippart A, Tze WJ, Crigler J. Portacaval shunt for glycogen storage disease: value of prolonged intravenous hyperalimentation before surgery. Surgery 1972;72(2):306–14.
10. Greene HL, Slonim AE, O'Neill JA, Jr, Burr IM. Continuous nocturnal intragastric feeding for management of type I glycogen storage disease. N Engl J Med 1976;294:1125–9.
11. Burr IM, O'Neill JA, Karzon DT, Howard LJ, Greene HL. Comparison of the effects of total parenteral nutrition compared to portacaval shunt on a patient with type I glycogen storage disease. J Pediatr 1974;85(6):792–5.
12. Bier DM, Leake RD, Haymond MW, Arnold KJ, Gruenke LD, Sperling MA, Kipnis DM. Measurement of "true" glucose production rates in infancy and childhood with 6,6-dideuteroglucose. Diabetes 1977;26(11):1016–23.
13. Fernandes J, Leonard JV, Moses SW, Odievre M, Di Rocco M, Schaub J, Smit GPA, Ulrich K, Durand P. Glycogen storage disease: recommendations for treatment. Eur J Pediatr 1988;147(3):226–8.
14. Chen YT, Cornblath M, Sidbury JB. Cornstarch therapy in type I glycogen storage disease. N Engl J Med 1984;310(3):171–5.
15. Crigler JF, Folkman JI. Glycogen storage disease: new approaches to therapy. Ciba Found Symp 1978;(55):331–51.

16. Rake J, Visser G, Labrune P, Leonard JV, Ullrich K, Smit GPA. Guidelines for management of glycogen storage disease type I—European Study on Glycogen Storage Disease Type I (ESGSD I). Eur J Pediatr 2002;161:112–9.
17. Wolfsdorf JI, Plotkin RA, Laffel LM, Crigler JF, Jr. Continuous glucose for treatment of patient with type 1 glycogen-storage disease: comparison of the effects of dextrose and uncooked cornstarch on biochemical variables. Am J Clin Nutr 1990;52(6): 1043–50.
18. Derks TGJ, Martens DH, Sentner CP, van Rijn M, de Boer F, Smit GPA, van Spronsen FJ. Dietary treatment of glycogen storage disease type Ia; uncooked cornstarch and/or continuous nocturnal gastric drip-feeding? Mol Genet Metab 2013;109(1):1–2.
19. Colonetti K, Bento dos Santos B, Nalin T, Souza CFM, Triplett E, Thiago Dobber P, Schwartz IVD, Roesch LFW. Hepatic glycogen storage diseases are associated to microbial dysbiosis. PLoS One 2019;14(4):e0214582.
20. Weinstein DA, Wolfsdorf JI. Effect of continuous glucose therapy with uncooked cornstarch on the long-term clinical course of type Ia glycogen storage disease. Eur J Pediatr 2002;161:35–9.
21. Kishnani PS, Boney A, Chen YT. Nutritional deficiencies in a patient with glycogen storage disease type Ib. J Inherit Metab Dis 1999;22(7):795–801.
22. Wolfsdorf JI, Holm IA, Weinstein DA. Glycogen storage diseases: phenotypic, genetic, and biochemical characteristics and therapy. Endocrinol Metab Clin North Am 1999;28(4):801–23.
23. Weinstein DA, Koeberl DD, Wolfsdorf JI. Inborn errors of metabolism: type I glycogen storage disease. In: Gruson ES, editor. National Organization of Rare Diseases Guide to Rare Disorders. Philadelphia, PA: Lippincott Williams & Wilkins; 2003:450–1.
24. Heller S, Worona L, Consuelo A. Nutritional therapy for glycogen storage diseases. J Pediatr Gastroenterol Nutr 2008;47:15–21.
25. Correia CE, Bhattacharya K, Lee PJ, Shuster JJ, Theriaque DW, Shankar MN, Smit GP, Weinstein DA. Use of modified cornstarch therapy to extend fasting in glycogen storage disease types Ia and Ib. Am J Clin Nutr 2008;88(5):1272–6.
26. Rousseau-Nepton I, Huot C, Laforte D, Mok E, Fenyves D, Constantin E, Mitchell J. Sleep and quality of life of patients with glycogen storage disease on standard and modified uncooked cornstarch. Mol Genet Metab 2018;123(3):326–30.
27. Ross KM, Brown LM, Corrado MM, Chengsupanimit T, Curry LM, Ferrecchia IA, Porras LY, Mathew JT, Weinstein DA. Safety and efficacy of chronic extended release cornstarch therapy for glycogen storage disease type I. JIMD Rep 2015;26:85–90.
28. Ross KM, Brown LM, Corrado MM, Chengsupanimit T, Curry LM, Ferrecchia IA, Porras LY, Mathew JT, Weinstein DA. Safety and efficacy of long-term use of extended release cornstarch therapy for glycogen storage disease types 0, III, VI, and IX. J Nutri Thera 2015;4(4): 137–42.
29. Fernandes J. The effect of disaccharides on the hyperlactacidaemia of glucose-6-phosphatase-deficient children. Acta Paediatr 1974;63(5):695–8.
30. Derks TGJ, Nemeth A, Adrian K, Arnell H, Roskjær AB, Beijer E, te Boekhorst S, Heidenborg C, Landgren M, Nilsson M, et al. Hepatic glycogen storage diseases: toward one global collaborative network. J Inborn Errors Metab Screen 2017;5:1–4.
31. Phillips A. More questions: 10 years later from glycogen storage disease patient support groups in Europe. Eur J Pediatr 2002;161(1): 102–5.
32. Kishnani PS, Austin SL, Abdenur JE, Arn P, Bali DS, Boney A, Chung WK, Dagli AI, Dale D, Koeberl D, et al. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. Genet Med [Internet] 2014;16(11):e1. Available from: https://doi.org/10.1038/gim.2014.128.
33. Bhattacharya K, Orton RC, Qi X, Mundy H, Morley DW, Champion MP, Eaton S, Tester RF, Lee PJ. A novel starch for the treatment of glycogen storage diseases. J Inherit Metab Dis 2007;30: 350–7.
34. Bhattacharya K. Investigation and management of the hepatic glycogen storage diseases. Transl Pediatr 2015;4(3):240–8.
35. Luat AF, Coyle L, Kamat D. The ketogenic diet: a practical guide for pediatricians. Pediatr Ann 2016;45(12):e446–50.
36. Derks TGJ, van Rijn M. Lipids in hepatic glycogen storage diseases: pathophysiology, monitoring of dietary management and future directions. J Inherit Metab Dis 2015;38:537–43.
37. Ontko JA, Johns ML. Evaluation of malonyl-CoA in the regulation of long-chain fatty acid oxidation in the liver. Evidence for an unidentified regulatory component of the system. Biochem J 1980;192(3):959–62.
38. Minarich LA, Silverstein J. Vitamin D update: shining light on the debate. Contemp Pediatr 2011;28(3):46–55.
39. Tsilianidis LA, Fiske LM, Siegel S, Lumpkin C, Hoyt K, Wasserstein M, Weinstein DA. Aggressive therapy improves cirrhosis in glycogen storage disease type IX. Mol Genet Metab 2013;109:179–82.
40. Melis D, Minopoli G, Balivo F, Marcolongo P, Parini R, Paci S, Dionisi-Vici C, Della Casa R, Benedetti A, Andria G, et al. Vitamin E improves clinical outcome of patients affected by glycogen storage disease type Ib. JIMD Rep. 2016;25:39–45.
41. Sentner CP, Hoogeveen IJ, Weinstein DA, Santer R, Murphy E, Steuerwald U, Beauchamp NJ, Taybert J, Laforêt P, et al. Glycogen storage disease type III: diagnosis, genotype, management, clinical course and outcome. J Inherit Metab Dis 2016;39(5):697–704.
42. Kishnani PS, Austin SL, Arn P, Bali DS, Boney A, Case LE, Chung WK, Desai DM, El-Gharbawy A, Haller R, et al. Glycogen storage disease type III diagnosis and management guidelines. Genet Med 2010;12(7):446–63.
43. Dagli AI, Weinstein DA. Glycogen storage disease type VI. In: Adam MP, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A,editors. Gene Reviews [Internet]. Seattle, WA: University of Washington, National Center for Biotechnology Information; 2009 [cited July 24, 2014]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK5941.
44. Bali DS, Goldstein JL, Fredrickson K, Rehder C, Boney A, Austin S, Weinstein DA, Lutz R, Boneh A, Kishnani PS. Variability of disease spectrum in children with liver phosphorylase kinase deficiency caused by mutations in the *PHKG2* gene. Mol Genet Metab 2014;111:309–13.
45. Goldberg T, Slonim A. Nutrition therapy for hepatic glycogen storage diseases. J Am Diet Assoc 1993;93(12):1423–30.
46. Weinstein DA, Correia CE, Saunders AC, Wolfsdorf JI. Hepatic glycogen synthase deficiency: an infrequently recognized cause of ketotic hypoglycemia. Mol Genet Metab 2005;87:284–8.
47. Santer R, Steinmann B, Schaub J. Fanconi–Bickel syndrome—a congenital defect of facilitative glucose transport. Curr Mol Med 2002;2:213–27.
48. Gupta N, Nambam B, Weinstein DA. Late diagnosis of Fanconi–Bickel syndrome: challenges with the diagnosis and literature review. J Inborn Errors Metab Screen 2016;4:1–6.
49. Fernandes J, Huijing F. Branching enzyme-deficiency glycogenosis: studies in therapy. Arch Dis Child 1968;43(229):347–52.
50. Leonard JV, Frances DE, Dunger DB. The dietary management of hepatic glycogen storage disease. Proc Nutr Soc 1979;38(3):321–4.
51. Slonim AE, Coleman RA, Moses WS. Myopathy and growth failure in debrancher enzyme deficiency: improvement with high-protein nocturnal enteral therapy. J Pediatr 1984;105(6):906–11.
52. Okechuku GO, Shoemaker LR, Dambska M, Brown LM, Mathew J, Weinstein DA. Tight metabolic control plus ACE inhibitor therapy improves GSD I nephropathy. J Inherit Metab Dis 2017;4:703–8.
53. Kishnani PS, Goldstein J, Austin SL, Arn P, Bachrach B, Bali DS, Chung WK, El-Gharbawy A, Brown LM, Kahler S, et al. Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2019;21(4):772–89.
54. Valayannopoulos V, Bajolle F, Arnoux JB, Dubois S, Sannier N, Baussan C, Petit F, Labrune P, Rabier D, Ottolenghi C, et al. Successful treatment of severe cardiomyopathy in glycogen storage disease type III with D,L-3-hydroxybutyrate, ketogenic and high-protein diet. Pediatr Res 2011;70:638–41.

55. Sentner CP, Caliskan K, Vletter WB, Smit GP. Heart failure due to severe hypertrophic cardiomyopathy reversed by low calorie, high protein dietary adjustments in a glycogen storage disease type IIIa patient. JIMD Rep 2012;5:13–6.

56. Dambska M, Labrador EB, Kuo CL, Weinstein DA. Prevention of complications in glycogen storage disease type Ia with optimization of metabolic control. Pediatr Diabetes 2017;18(5): 327–31.