Annu. Rev. Nutr. 1993. 13:83–109

NUTRITIONAL MANAGEMENT OF GLYCOGEN STORAGE DISEASE

P. H. Parker
Department of Pediatrics, University of Mississippi, Jackson, Mississippi 39216

M. Ballew
Department of Pediatrics, Vanderbilt University, Nashville, Tennessee 37232

H. L. Greene
Meade Johnson Research Center, Evansville, Indiana 47721

KEY WORDS: dietary therapy glycogenosis, glycogenoses therapeutics

CONTENTS

0199-9885/93/0715-0083$02.00

INTRODUCTION

In 1929, the initial clinical and pathologic recognition of glycogen storage disease (GSD) affecting the liver and kidney was made by von Gierke (85). Three years later, a second type of glycogen storage disease involving not only the liver and kidney but most other organs as well was described by Pompe (69). In 1952, Cori & Cori found a deficiency of glucose-6-phosphatase activity in patients with von Gierke's disease (15). Since then the glycogenoses have been classified by the type of enzymatic defects and the primary organs involved. Abnormalities involving most every step of glycogen

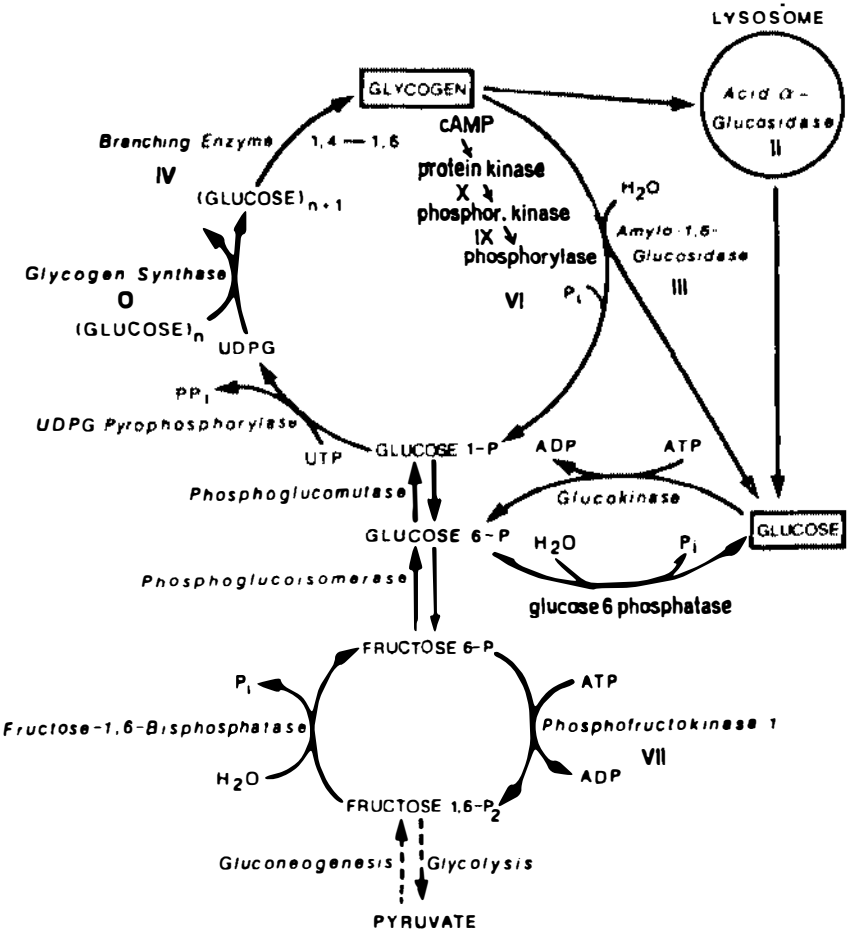

Figure 1 Diagram of the pathway of liver glycogen metabolism and its enzymic defects in various types of glucose storage disease.

Table 1 Classification of glycogen storage diseases (GSD)s

Type	Enzyme affected	Primary organ involved	Manifestations
0	Glycogen synthetase	Liver	Hypoglycemia, hyperketonemia, FTT[a] early death
Ia	Glucose-6-phosphatase	Liver	Enlarged liver and kidney, growth failure, fasting hypoglycemia, acidosis, lipemia, thrombocyte dysfunction
Ib	Microsomal membrane G-6-P transporter	Liver, PMN leucocytes	As in Ia; in addition, recurrent neutropenia, bacterial infections
Ic	Microsomal membrane PP_i transporter	Liver	As in Ia
II	Lysosomal acid α-glucosidase (acid maltase)	All lysosome-containing organs	Infantile form: early-onset progressive muscle hypotonia, cardiac failure, death before 2 years; juvenile form: later-onset myopathy with variable cardiac involvement; adult form: limb-girdle muscular dystrophy-like features
III	Amylo-1,6-glucosidase (debrancher enzyme)	Liver, skeletal muscle, heart	Fasting hypoglycemia; hepatomegaly in infancy in some myopathic features; rarely, clinical cardiac features
IV	Amylo-1,4-1,6-*trans*-glucosidase (brancher enzyme)	Liver	Hepatosplenomegaly, cirrhosis
V	Muscle phosphorylase	Skeletal muscle	Exercise-induced muscular pain cramps and progressive weakness, sometimes with myoglobinuria
VI	Liver phosphorylase	Liver	Hepatomegaly, mild hypoglycemia, good prognosis
VII	Phosphofructokinase	Muscle, RBC	As in V; in addition, enzymopathic hemolysis
IXa	Phosphorylase b kinase	Liver	As in VI.
IXb	Phosphorylase b kinase	Liver, muscle (?), leucocytes	Hepatomegaly, sex-linked inheritance
IXc	Phosphorylase b kinase	Liver, muscle, blood cells	Hepatomegaly, autosomal inheritance
X	Cyclic AMP dependent kinase	Liver, muscle	Hepatomegaly

[a] FTT, failure to thrive; PMN, polymorphonuclear leucocytes.

synthesis and degradation have been described and are illustrated in Figure 1. A classification system of GSDs—the nomenclature of various types, enzyme or protein deficiency, organ involvement, and a summary of the main clinical features—is provided in Table 1. In spite of differences in the specific enzyme defects, most of the syndromes are not readily distinguishable on clinical grounds alone, and tissue analyses for glycogen content and enzymatic activity are necessary to confirm the diagnoses (41, 46).

In recent years, a better understanding of the pathophysiology of the GSDs has led to more effective therapy and an improvement in the quality of life and prognosis in these patients. However, increasing longevity has been accompanied by new problems that require further investigation and new therapeutic approaches. Because the greatest advances have been made in treatment of type I glycogen storage disease (GSD-I), we review this disorder and its management in detail. Special emphasis is placed on both the pathophysiologic mechanisms present in GSD-I and their response to nutritional therapy. In addition, specific practical dietary management of GSD-I is discussed. Finally we briefly review other types of GSD that may benefit from dietary therapies.

TYPE I GLYCOGEN STORAGE DISEASE

Type I glycogen storage disease (GSD-I) is due to a deficiency in the activity of glucose-6-phosphatase in the liver, kidney, and small intestine. This form of glycogenosis is transmitted in an autosomal recessive manner and accounts for about one fourth of all cases diagnosed (27, 36).

Type I GSD has been divided into at least five subtypes (IA, IASP, IB, IC, ID). This system of classification is based on the finding that for some patients in vitro activity of glucose-6-phosphatase is nearly normal, whereas in vivo activity is absent. Our understanding of the glucose-6-phosphatase enzyme system has expanded considerably and has been recently reviewed by Burchell & Waddell (9). The recognition of various types may help explain the wide variations in severity between patients and the presence of unusual features such as neutropenia in type IB. Since the different types have similar metabolic changes and a similar response to treatment, a general discussion of type IA (designated GSD-I) is presented.

Most enzymatic defects in the GSDs involve either the degradation of glycogen to glucose-6-phosphate or, rarely, the synthesis of glycogen from glucose-6-phosphate. In patients with GSD-I, the absence of activity of the gluconeogenic enzyme, glucose-6-phosphatase, results in an inability to release normal amounts of glucose from glucose-6-phosphate. The absence of enzymatic activity at such a crucial metabolic "crossroads" results in

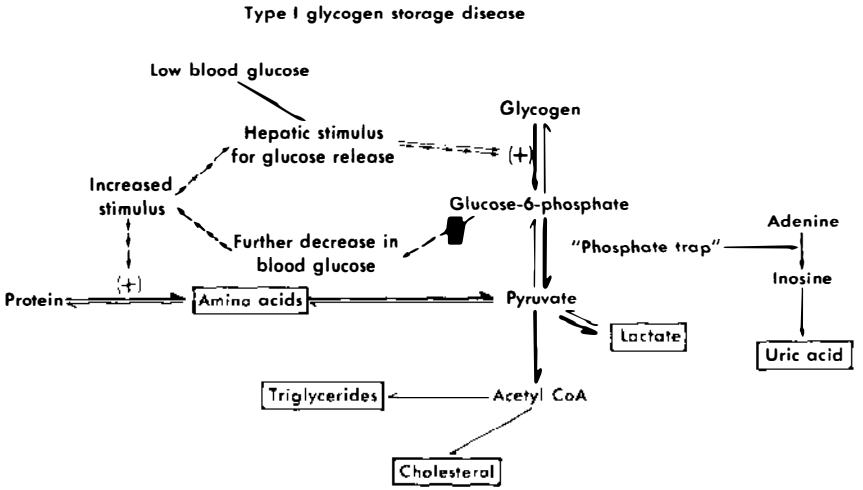

Figure 2 Biochemical basis for the primary laboratory findings in patients with glucose-6-phosphatase deficiency (*indicated by the solid rectangle*). The increased production of glucose-6-phosphate that results from continuous stimulation of glycogen breakdown apparently increases glycolysis, which in turn results in a net increase (*indicated by dark arrows*) in the production of lactate, triglyceride, cholesterol, and uric acid. Both glycogenolysis and gluconeogenesis are involved in the overproduction of substrate.

many of the biochemical and clinical features of GSD-I that are unique among the glycogen storage diseases. For example, lactic acidosis, hyperlipidemia, hyperuricemia, platelet dysfunction, and hepatic adenomas accompany GSD-I but are not seen with the other glycogenoses. The study of mechanisms whereby deficiency of glucose-6-phosphatase activity results in such striking aberrations in carbohydrate, lipid, and purine metabolism has been instrumental in the development of effective forms of therapy for this disorder (Figure 2).

Blood Glucose Changes

The most consistent and life-threatening feature of GSD-I is the hypoglycemia that occurs after relatively short periods of fasting. A decrease in blood glucose to less than 70 mg/dl almost always occurs after a 2- to 4-hr fast, and it is not uncommon to observe 6- to 8-hr fasting levels of 5 to 10 mg/dl. In normal individuals, blood glucose levels are maintained within a relatively narrow range by agents such as glucagon, which release glucose from glycogen, or by gluconeogenesis (13). In GSD-I both glycogenolysis and gluconeogenesis occur normally in response to hypoglycemia; however, because of an absence

of glucose-6-phosphatase, glucose is not released from glucose-6-phosphate and blood glucose levels continue to decline. These patients have an appropriate hormonal (glucagon and insulin) response to changes in blood glucose concentrations (41, 79). In the absence of exogenous glucose, the blood glucose continues to decline and further hormonal stimulus occurs, resulting in far-reaching effects on various metabolic pathways.

Patients with untreated GSD-I do not always manifest the characteristic clinical features of hypoglycemia and may function completely normally with levels of blood glucose below 20 mg/dl. This adaptation to hypoglycemia has been attributed to high levels of lactate, which can serve as an alternate fuel for brain metabolism (17, 34). When patients are metabolically and hormonally stabilized with adequate therapy, their clinical response to hypoglycemia is the same as seen in normal individuals (27, 64).

As glucose-6-phosphatase provides the final common pathway for glucose production from both glycogenolysis and gluconeogenesis, one would expect a block at this step to result in a major reduction in endogenous glucose production. In 1969, Havel et al reported that two adults with GSD-I showed near-normal basal rates of glucose production (34). This observation has been verified in patients of all ages by several investigators (53, 70, 81). Although the source of this endogenous glucose production is currently unknown, these studies have important therapeutic implications. (*i*) Patients with GSD-I can release glucose into the circulation at close to normal basal rates but cannot increase glucose release during fasting, in response to exercise, or following a pharmacologic dose of glucagon. Thus, their maximal rate of glucose production is fixed and substantially below that present in normal individuals. (*ii*) Maximal glucose production rates are variable between patients and related to the individual patient's tendency for fasting-induced hypoglycemia and the severity of the clinical illness. (*iii*) Endogenous production of glucose is not inhibited unless an exogenous source of glucose is provided at a rate of 8 mg/kg per minute, an amount that maintains blood glucose levels at about 90 mg/dl.

Lactic Acid Changes

Under normal circumstances, most circulating lactate is generated by muscle glycolysis during exercise and is efficiently metabolized by the liver (13). In patients with GSD-I most of the circulating lactate is generated by hepatic glycolysis (75). In the latter case, apparently hepatic stimulation to release glucose from glycogen is combined with inefficient gluconeogenesis. The excessive glucose-6-phosphate formed during glycogenolysis cannot be hydrolyzed to free glucose because of the lack of glucose-6-phosphatase activity

and is diverted through the glycolytic pathway. The result is increased lactate formation.

Hyperlipidemia

Elevation of plasma lipids is a consistent and striking abnormality: Triglyceride levels reach 6000 mg/dl and cholesterol levels 400–600 mg/dl (19, 27, 49). Free fatty acid levels are also usually elevated. Xanthomas typically appear over extensor surfaces usually around puberty, but they may also develop in childhood.

As with lacticemia, elevated triglyceride and cholesterol levels appear to be a consequence of increased rates of glycogenolysis and glycolysis. In GSD-I excessive hepatic glycolysis increases hepatic nicotinamide-adenine dinucleotide (NADH), nicotinamide-adenine dinucleotide phosphate (NADPH), and acetyl coenzyme A (CoA), three compounds important in fatty acid and cholesterol synthesis (75). The increases in glycerol-3-phosphate and acetyl CoA generated by the glycolytic pathway, together with elevated levels of reduced cofactors, could sustain an increased rate of triglyceride and cholesterol synthesis (20, 65). In addition to this apparent increased rate of lipid synthesis, hypoglycemia stimulates lipolysis from peripheral lipid stores. This further augments hyperlipidemia and hepatic steatosis by increasing circulating free fatty acids (19, 20, 44, 65).

The institution of a strict dietary regimen to maintain near-normal blood glucose levels results in a marked reduction in serum lipids. However, most patients with GSD-I have had persistent hypertriglyceridemia, even after years of treatment (28, 58). While this phenomenon appears to result primarily from increased lipid synthesis, other patients have shown decreased levels of postheparin lipoprotein lipase and lipid clearance in GSD-I (20, 34).

A detailed analysis of plasma lipids in 12 patients with GSD-I was recently published (30). All patients had triglyceride levels between 1440 and 6120 mg/dl before treatment. After treatment to maintain blood glucose levels of 75–85 mg/dl, triglyceride levels were between 189 +/–31 and 510 +/– 60 mg/dl in 11 patients. One patient, whose triglyceride levels remained elevated despite dietary treatment, was given several treatment strategies that have been useful in the management of hyperlipidemia. Clofibrate, niacin, and fish oil resulted in a temporary decline in triglyceride levels. However, lovastatin, a 3-hydroxy-3-methylglutaryl CoA reductase inhibitor, resulted in a substantial increase in triglyceride levels, although the serum cholesterol decreased significantly. The mechanism of these changes in response to lovastatin has not been studied but might be explained by the possible diversion of acetyl CoA from cholesterol synthesis to fatty acid and triglyceride synthesis.

Combined treatment with clofibrate and niacin provided a more sustained reduction in triglyceride levels; however, the tendency to become resistant to pharmacologic intervention, together with possible complication from these agents, may prevent their long-term use.

In addition to the hyperlipidemia in patients with GSD-I, Levy et al suggested that the low-fat diet used in treatment may promote an essential fatty acid (EFA) deficiency that could contribute to impaired growth (57). No other clinical signs of EFA deficiency were noted in these patients. To evaluate the possibility of EFA deficiency, the plasma fatty acid composition and urinary prostaglandin excretion was evaluated in six patients with GSD-I (30). Increased percentages of 16:0 and $16{:}_{w7}$ and decreased percentages of $18{:}2_{w6}$ and $20{:}4_{w6}$ were found. These changes are generally characteristic of EFA deficiency. However, although the $20{:}3_{w6}/20{:}4_{w6}$ ratio was increased, there was no increase in $20{:}3_{w9}$, the characteristic fatty acid present in EFA deficiency, in either these patients or those of Levy. The most likely explanation for the changes in plasma fatty acids in GSD-I is the increased rate of hepatic lipogenesis. Havel et al demonstrated a high rate of synthesis and release of free acids in triacylglycerols, predominantly of 16:0 and $16{:}1_{w9}$, which could stimulate triglyceride and lipoprotein production by the liver (34). Indeed, the increased levels of 16:0 and $16{:}1_{w9}$ observed in these patients are consistent with the suggested increase in hepatic fatty acid synthesis in GSD-I. An absence of EFA deficiency is further supported by the normal excretion of prostaglandin E-M (PGE-M) in these patients (21).

Hyperuricemia

Although blood levels of uric acid and the tendency to develop nephropathy and gouty arthritis vary in different patients, those surviving to puberty often have gouty complications (18, 39). The hyperuricemia was originally attributed to the increased levels of blood lactate and lipids, which competitively inhibit urate excretion at a renal level (18, 42). However, the high level of urate excretion together with the increased rate of incorporation of C^{14}-L-glycine into plasma and urinary urate indicates that an increased rate of purine synthesis de novo is probably more important than a decrease in urate excretion in the genesis of hyperuricemia (50, 54). At least two mechanisms can influence the rate of purine synthesis: (*i*) alteration of the precursor concentration and (*ii*) alteration of the end product, or purine concentration (31, 71). Supporting the former mechanism is the observation that two substrates, phosphoribosylpyrophosphate (PRPP) and glutamine, are necessary for the first committed reaction of purine synthesis. This reaction transfers the amine from L-glutamine to PRPP to form 5-phosphoribosyl-1-amine and is apparently the rate-limiting step for the entire sequence of purine synthesis (Figure 3). Blood levels of glutamate and glutamine obtaincd from hyperuricemic patients

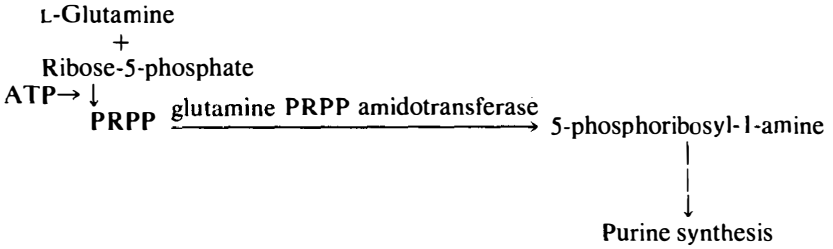

Figure 3 Purine synthesis as a result of increased precursor concentrations.

with GSD-I are three- to eightfold higher than are values obtained after urate is normalized by glucose infusion (29). The high levels of glucose-6-phosphate produced during periods of hypoglycemia and excessive glycogenolysis may increase hexose monophate shunt activity and increase synthesis of ribose-5-phosphate, the second important substrate in purine synthesis (18, 40). This suggests that an apparent increased availability of purine precursors, glutamine, and ribose-5-phosphate may cause a secondary increase in PRPP and thus increase the rate of purine synthesis. Studies using human leukocytes indicate, however, that an increase in availability of glutamine and ribose-5-phosphate does not necessarily increase the generation of PRPP (7). If this is true in the liver, then low concentration of intracellular purine may be more important in increasing the rate of purine synthesis in patients with GSD-I.

In support of the second mechanism of hyperuricemia, low levels of purine ribonucleotides would favor an increase in the rate of purine biosynthesis by releasing glutamine pyrophosphate-ribose-phosphate amidotransferase from end-product inhibition (37). Although hepatic nucleotide levels during hypoglycemic episodes have not been measured directly, indirect evidence suggests that hypoglycemia can reduce adenyl ribonucleotide concentrations in GSD-I (26). Such a reduction in ATP has been shown to favor the rapid degradation of adenyl or guanyl ribonucleotides to inosine, xanthine, and uric acid (73). These reactions are also promoted by low levels of intracellular phosphate, which apparently occur through "phosphate trapping" of the phosphorylated intermediates of the Emden-Meyerhoff pathway (22, 73). These observations suggest that the increase in uric acid production is due to recurrent episodes of hypoglycemia, which result in compensatory glucagon release (Figure 4). Glucagon stimulates glycogen degradation to glucose-6-phosphate, and an absence of phosphatase activity results in a phosphate-trapping effect and lowering of ATP levels, which in turn promotes degradation of preformed purines to uric acid. Finally, the decrease in purine concentration promotes a high rate of purine biosynthesis.

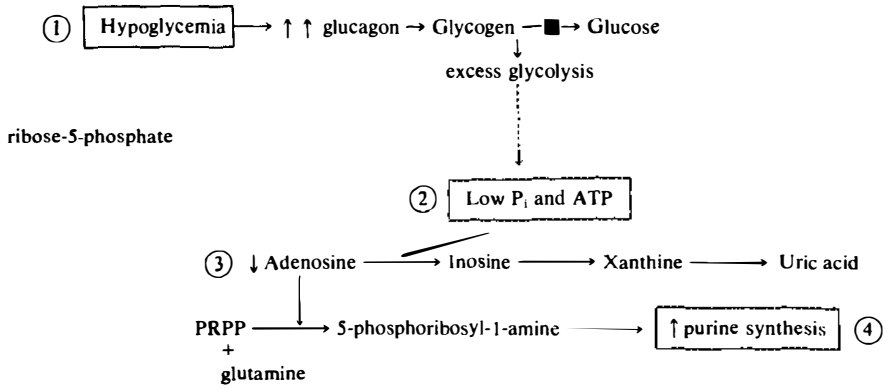

Figure 4 Purine synthesis as a result of increased purine degradation.

Hypophosphatemia

Low levels of circulating phosphate are not an invariable finding but are often present during periods of hypoglycemia and acidosis. This phenomenon is thought to be created by the phosphate trap resulting from glucose-6-phosphatase deficiency. Because of their inability to release inorganic phosphate, liver cells must take up phosphorus from the plasma with a consequent decline in circulating phosphate levels (22) (Figure 5). In addition, a relative metabolic block at the aldolase step of glycolysis would be expected because of the progressive increase in NADH formed during the initial phase of the reaction cascade from glucose-6-phosphate to pyruvate. This metabolic block would

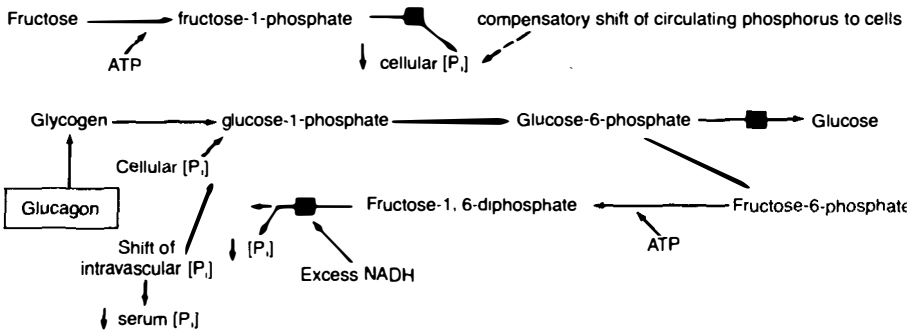

Figure 5 Serum phosphate changes in GSD-I.

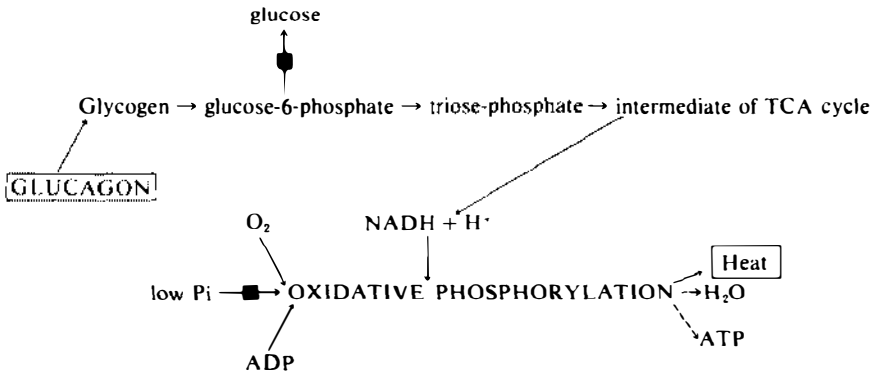

Figure 6 Uncoupling of oxidative phosphorylation in GSD-I.

promote even more phosphate-trapping with a further shift of circulating phosphate to the intracellular pool. As the phosphate is lost from the metabolic intermediates, a compensatory return of phosphate back into the circulation would be expected. Hypophosphatemia may also explain the recurrent episodes of fever occasionally seen in patients with GSD-I during episodes of severe hypoglycemia and acidosis. The febrile response may represent an uncoupling of oxidative phosphorylation secondary to a lack of intracellular Pi. For example, following exogenous glucagon administration to stimulate hypoglycemia, some patients became febrile with severe lactic acidosis and hypophosphatemia (22). It has been suggested that the burst of glycolysis produced by glucagon resulted in a high level of reduced cofactors, which normally produce high-energy phosphates. Owing to limited levels of intracellular phosphate, oxidative phosphorylation would be expected to result in heat production rather than chemical energy in the form of ATP (Figure 6).

Platelet Dysfunction

Frequent nosebleeds and a hemorrhagic tendency during surgical procedures have been observed in patients with GSD-I. In the majority of these patients a prolonged bleeding time, abnormal platelet aggregation, reduced platelet adhesiveness, and an impaired ability of platelets to release ADP in response to collagen or epinepherine were demonstrated (1, 14, 23). These defects in platelet function may be secondary to systemic metabolic abnormalities such as hypoglycemia, hyperlipidemia, and hyeruricemia. Czapek et al have shown that the platelet dysfunction in GSD-I can be corrected by improving the metabolic state of the patients with parenteral or nasogastric therapy (16). Thus, while the specific mechanism causing the abnormal platelet function is

not clearly defined it is correctable by maintenance of a blood glucose concentration within the normal range (70–100 mg/dl).

Growth Impairment

Children with GSD-I are of short stature but without disproportionate head size or extremity length. Bones may be osteoporotic, and some patients have delayed bone age. The mechanisms leading to these changes are not clear. Thyroid hormone and growth hormone levels are normal or increased (29, 41). Measurement of caloric-protein intake in GSD-I indicates adequate caloric consumption. Chronic lactic acidosis and reversal of the insulin-glucagon ratio have been proposed as factors in preventing normal growth. Recently, Yudkoff et al studied whole-body protein synthesis in four patients with GSD-I (88). A depletion of their amino acid pool, presumably due to excessive protein catabolism associated with decreased protein synthesis, was found. This process was reversed when glucose was administered at 150% of the expected normal glucose production rate. This catabolic state, which exists in the presence of insufficient glucose administration, may contribute to the poor growth in these patients.

Hepatic Adenoma and Carcinoma

The majority of patients with GSD-I who are more than 20 years old have adenomatous nodules in their liver. These adenomas usually develop during the second decade of life, but may occur in younger patients. A number of patients have had a malignant degeneration of these adenomas to hepatocellular carcinoma, most often after 30 years of age (43, 59, 68, 74). The mechanism causing these adenomas or their malignant change is unknown. Strict adherence to dietary therapy may reduce the tendency for adenoma formation, but in the authors' experience all patients eventually develop adenomas (66). This suggests that chronic stimulation of the liver by hepatotrophic agents (glucagon and others), which increase blood glucose level, may be important in the genesis of the adenomas.

Renal Involvement

The kidneys are enlarged in GSD-I and have no glucose-6-phosphatase activity. The elevated serum level of uric acid in GSD-I has been associated with the development of uric acid nephropathy (12, 18, 54). This complication has decreased considerably with improved dietary therapy, which results in decreased blood uric acid levels, and occasional allopurinol administration. Recently, cases of chronic renal disease with a progressive glomerulosclerosis have been described in older patients with GSD-I (10). The renal disease in these patients may progress to renal failure and death. Although the cause of the lesion is unclear, apparently the incidence is lowered by good metabolic

control, since none of the authors' nine patients, ages 25 to 34, show renal abnormalities.

NUTRITIONAL MANAGEMENT OF GSD-I

The objective of dietary therapy in GSD-I is to provide a constant source of carbohydrate sufficient to maintain blood glucose levels between approximately 70 and 100 mg/dl. Preventing fluctuations of greater magnitude minimizes organic acidemia, hyperlipidemia, hyperuricemia and maximizes achievement of full growth potential. In fact, virtually all clinical manifestations of the disorder can be reversed through appropriate nutritional management. This objective may be achieved through a combination of a nocturnal nutrient infusion and frequent daytime feedings of a high starch diet in which raw cornstarch is used to provide a steady, "time-release" source of glucose.

Traditionally, the Recommended Dietary Allowances (RDA) have been used as a guideline to estimate the initial energy requirements. While no data indicate that energy requirements for individuals with GSD-I differ from the norm, this approach may be inappropriate for predicting the needs of individuals, particularly when disease imposes the potential for altered nutrient utilization. Initially, infants and children with GSD-I are often below the fiftieth percentile for age on National Center for Health Statistics growth charts; however, they are often above average weight for height. Thus, alterations in body composition limit the applicability of standard equations for predicting energy requirements in this disorder.

Ideally, the calorie content of the GSD-I diet should be determined through actual measurement of 24-hr energy expenditure. Unfortunately, metabolic chambers are usually available only in research settings. However, portable metabolic carts that determine energy requirements through measurement of O_2 consumption and CO_2 production have become increasingly available in the past ten years and may prove useful in the management of this group of patients.

The 1989 RDA are used to establish protein requirements for the individual with GSD-I. These age-specific standards are used as a guideline to ensure that minimum daily protein requirements are met.

Nocturnal Nutrient Infusion

Once energy requirements are established, this component of nutritional therapy is planned. Nutritionally complete elemental formulas in which glucose polymers are the predominant energy source are ideal for this purpose. The formula provides 30–40% of total energy needs. Infusion rate is calculated based on hepatic glucose production rate, which, in the authors' experience, ranges from 4 to 6 mg/kg per minute during sleep. This usually

requires an 8- to 10-hr infusion period beginning within 3 hr of the last daytime feeding and ending 30 minutes after the first meal the following morning to avoid precipitous declines in blood glucose levels. The need for consistent delivery of glucose mandates the use of pump-assisted infusion, and it is essential that the enteral feeding pump be equipped with an alarm system in the event that tube occlusion, power failure, or other problems interrupt the infusion during the night (19). Calculation of a nocturnal nutrient infusion is shown in Table 2.

Various commercial elemental formulas have been used successfully and include Criticare HN®, Tolerex®, Vital HN®, and Vivonex TEN®. Other elemental formulas of lower osmolality for improved gastrointestinal tolerance are now available. Unfortunately, the high fat content of these formulas limits their applicability in GSD, since fat does not contribute to blood glucose maintenance. Pregestimil® and Prosobee®, two infant formulas that contain glucose oligosaccharides as the sole carbohydrate source, are used in children less than one year of age (19).

Table 2 Calculation of a GSD-I diet

Patient: 4-year old female

Weight: 16 kg (50th percentile); height: 37½ inches (5th percentile); average weight for height: 14 kg
Predicted energy needs: 1260 kcal/day
Proteins needs: 15–18 gm/day
Nocturnal nutrient infusion
Criticare HN: 1.06 kcal/cc; 220 gm CHO/L; 38 gm pro/L
1260 kcal × 25% = 318 kcal
Volume required: 300 cc
Infusion rate: 30 cc/hr × 10 hr (6.9 mg glucose/kg/min)
Daytime feedings
Remaining energy needs: 942 kcal
Carbohydrate: 942 × 65% = 612 kcal (153)
Protein: 942 × 15% = 141 kcal (35 gm)
Fat: 942 × 20% = 188 kcal (21 gm)

ADA exchanges	Carbohydrate	Protein	Fat
10 starch/bread	150	30	10
2 meat (lean)	—	14	6
1 fat	—	—	5
Total (gm)	150	44	21
kcal/gm	×4	×4	×9
Total (kcal)	600	176	189
Actual nutrient distribution	62%	18%	20%

Nocturnal nutrient infusions should be instituted in a closely monitored setting where serial measurements of blood glucose, lactic acid, uric acid, and triglycerides taken at 3- to 4-hr intervals can be used to evaluate efficacy of therapy. Infants and small children may experience improved gastrointestinal tolerance if formula is prepared at 20-kcal/oz concentration, However, if higher caloric density (i.e. 30 to 40 kcal/oz) is tolerated, urinary frequency during the infusion may be diminished. A number of investigators have successfully utilized uncooked cornstarch to avoid nocturnal infusions in patients at all ages, including infants (11, 87). In the authors' experience, growth rates were less with the raw starch regimen than with nocturnal infusions. Thus, while cornstarch feedings may be beneficial in some patients, careful monitoring of blood glucose levels is essential to ensure that treatment is optimal for individual patients. Once growth potential is achieved and glucose requirements decrease, cornstarch feedings may be used in place of the nocturnal nutrient infusion in most patients.

Daytime Feedings

The remainder of the calculated energy requirements is provided in small, high starch meals administered every 3 hr or as frequently as needed to maintain desired blood glucose levels between approximately 70 and 100 mg/dl.

Carbohydrate, supplied primarily in the form of starch, should provide 60–70% of the calories in daytime meals. Establishing carbohydrate content of daytime feedings at 8 to 9 mg/kg per minute has proven successful in achieving adequate metabolic control (19).

Raw cornstarch, which provides a gradual and sustained increase in blood glucose, may be administered with or between meals to achieve carbohydrate intake goals. Quantities equivalent to 1.75–2.5 gm cornstarch/kg (1 tablespoon = 10 gm cornstarch) given every 4 hr, or any amount needed to achieve desired metabolic response, may be mixed in relatively small quantities of water or sugar-free noncarbonated beverages. Rice cereal may be used as an alternative in infants who do not tolerate cornstarch feedings. Experiments using glucose and glucose polymers (Polycose® and Moducal®) have produced less favorable results. Both are rapidly absorbed, resulting in significant elevation of blood glucose. Subsequently, a rapid decline due to substantial insulin output occurs when blood glucose concentration exceeds 90 mg/dl.

Grain products and starchy vegetables should be the predominant sources of carbohydrate in daytime feedings, as the sugars contained in these foods are broken down entirely to glucose (33). Vegetables used in limited quantities are considered "free" choices. Additional benefits may be realized by including foods with high dietary fiber content. In the late 1970s, Jenkins et

al demonstrated that dietary fiber reduced postprandial blood glucose in patients with diabetes mellitus (51). These findings have been confirmed by others, and a comprehensive review of this subject was published by Anderson et al in 1987 (3). Soluble dietary fibers such as pectin and guar gum have been shown to have the most favorable effect on blood glucose response. The mechanism of action is thought to be related to their ability to delay glucose absorption in the proximal small intestine. In GSD-I, this delay theoretically minimizes peaks in blood glucose concentration and the subsequent rapid lowering of blood sugar because of reactive insulin release.

While the ingestion of fructose and galactose does not exert a toxic effect in GSD-I, the metabolic defect associated with this disorder prevents their conversion to glucose. Thus, foods containing fructose or galactose contribute less to the prevention of hypoglycemia than do grains and starches. Also, liberal intake of these sugars predisposes to inadequate starch intake. Therefore, fruits, juices, table sugar, and dairy products are limited but not omitted from the diet.

Dietary protein should provide 10–20% of total energy intake in daytime meals. Overall intake of protein from meat, poultry, fish, and eggs should meet the 1989 RDA based on age of the individual. Commercial enteral formulas used in the nocturnal nutrient infusion also contribute to the high quality protein content of the diet.

Fat should provide no more than 20–25% of calories in daytime feedings. Although this nutrient contributes little to elevations of cholesterol and triglycerides seen in GSD-I, it has no measurable effect in preventing hypoglycemia. Unrestricted use of fat can be detrimental if it replaces starch in the diet or contributes to excessive caloric intake resulting in obesity.

Long-term restriction of foods containing fructose and galactose results in inadequate intake of calcium and vitamin C. A portion of the deficits will be supplied by the formula used for nocturnal feeding. Supplementation with an appropriate multivitamin preparation and with calcium to meet the RDA for age group is recommended.

Patient Education

Education of the patient and caregivers should be initiated as soon as the diagnosis of GSD-I is confirmed. As with any modified diet, thorough understanding of the rationale for dietary modifications will enhance compliance. Clearly conveying priorities concerning dietary management facilitates appropriate choices by the patient and caregivers when the diet cannot be followed to perfection. For example, adhering to the meal schedule and intake of high starch foods is much more important in day-to-day treatment than the need to completely avoid foods containing fructose and galactose. The dietitian can help alleviate unnecessary anxiety if this information is clearly conveyed at the beginning of the teaching session.

Detailed guidelines on the management of home enteral nutritional support have been published elsewhere (19, 24). Instruction manuals and educational pamphlets are also readily available from formula and equipment manufacturers to facilitate training in this aspect of nutritional therapy. Instructions should include technique for tube placement and removal since most patients with GSD-I prefer to be completely free from the apparatus during the day.

Food exchange lists for the GSD-I diet were made available in 1984 (19). However, the most recent edition of the "Exchange Lists for Meal Planning" published by the American Diabetes Association and the American Dietetic Association in 1986 is an appropriate tool for teaching principles of meal planning. Information regarding the cornstarch equivalent of a bread/starch food choice (2 tablespoons cornstarch = 1 exchange) should be added to the exchange lists. Foods containing increased amounts of fiber as well as those of low fat content are highlighted to encourage frequent inclusion in the diet. Restriction of fructose and galactose can be accomplished simply by limiting choices from the fruit list, the milk list, and "Food for Occasional Use." Sample menus are shown in Table 3.

Finally, patients and caregivers should be educated on recognition and management of hypoglycemia. Symptoms of mild hypoglycemia include sweating, shakiness, irritability, and hunger and usually occur following a missed meal, an unusual amount of physical activity or during gastrointestinal illness. The condition may progress rapidly to unconsciousness if steps are not taken to raise blood glucose.

Early signs of hypoglycemia are best treated with administration of raw cornstarch (15–30 gm or 1.5 to 3 tablespoons) or cooked wheat starch (two to four crackers or 1/2 to 1 slice of bread). Overly concerned parents or children have been known to administer glucose or polysaccharides (corn syrup, Polycose, or Moducal) so frequently that rapid shifts in blood glucose between hypo- and hyperglycemia have occurred. However, in the event of severe hypoglycemia, these preparations may be necessary to achieve a more rapid increase in blood sugar. In such an instance, one teaspoon of powdered or two teaspoons of liquid glucose polymer per 30 pounds of body weight is usually sufficient to raise blood glucose by 30–40 mg/dl. If necessary, corn syrup containing no added sucrose (two teaspoons per 30 pounds) may be given. If neither is available, sweetened carbonated beverages or fruit juice may be given, but these have less effect on blood sugar since fructose cannot be converted to glucose in GSD-I.

Patients should be reevaluated initially after six months and annually thereafter, preferably in the hospital setting. During the first two days of hospitalization, diet and tube feedings should be administered exactly as reported to have been given at home. Effects on blood glucose are monitored and therapy is altered accordingly. Adjustments in nutrient intake to meet

Table 3 Meal pattern and menu for 4-year-old with GSD-I

Meal pattern	Day 1	Day 2	Day 3
7:30 A.M.			
2 starch/bread	2 slices whole grain toast	1 cup oatmeal, cooked	1 fat-free waffle
⅓ fat	1 tsp diet margarine	1 tsp diet margarine	2 tbsp artif. sweet syrup
Free choices	2 tsp artif. sweet jelly	Brown sugar substitute	8 oz ½% milk[a]
	4 oz orange juice[a]	1 oz apple juice[a]	
10:00 A.M.			
2 starch/bread	12 oz cornstarch beverage[b]	12 oz cornstarch beverage[b]	12 oz cornstarch beverage[b]
Free choices			
12:30 P.M.			
2 starch/bread	6 saltine crackers	15 baked tortilla chips	¼ of 10 inch cheese pizza[c]
1 meat	10 ¾ oz can chunky soup	Tuna salad sandwich: 2 slices low calories, high fiber bread	1 cup lettuce salad
⅓ fat	Diet soft drink	¼ cup tuna packed in water	2 tbsp low calorie ranch dressing
Free choices		1 tsp reduced calorie mayonnaise	Diet soft drink
		Celery, chopped	
		8 oz ½% milk[a]	
3:00 P.M.			
2 starch/bread	3 cups popcorn, with butter-flavored seasoning	¾ oz pretzels	18 reduced fat cheese crackers
Free choices	6 oz cornstarch beverage[b]	6 oz cornstarch beverage[b]	6 oz cornstarch beverage[b]
6:00 P.M.			
2 starch/bread	½ cup lima beans cooked	1 medium corn on cob	⅔ cup rice, cooked
1 meat	1 dinner roll, plain	1 hamburger bun, small	1 chicken drumstick, baked
⅓ fat	1 oz pork tenderloin, grilled	1 oz lean hamburger patty	½ cup steamed broccoli
Free choices	2 tsp brown gravy	1 tsp reduced calorie mayo	Butter Buds®
	½ cup carrots steamed	Mustard	½ cup sliced peaches[a]
	Butter Buds	I tbsp catsup	Water
	8 oz ½% milk[a]	Butter Buds	
		1 cup artif. sweet. gelatin	
		2 tbsp whipped topping	
		Diet soft drink	

[a]Limited amounts of dairy products, fruits and juices are included to increase nutritional value of the diet and to enhance acceptance.

[b]Cornstarch beverage contains 2 tbsp raw cornstarch per 6 oz water or artificially sweetened fruit drink.

[c]Contains entire daily fat allowance.

changing requirements for growth with age and activity should also be made at this time.

A lifetime need for dietary modifications and specialized nutritional therapy imposes psychological demands on the patient, especially during adolescence. The dietitian should strive to accommodate food preferences and lifestyle as much as possible to enhance compliance without sacrificing metabolic control, particularly during stressful times. The Association for Glycogen Storage Disease is an excellent source of additional information and support for patients and family members affected by this disease.

Prognosis

While long-term follow-up of the results of aggressive dietary therapy is not complete, a ten-year follow-up indicates that these patients have many fewer problems than they had prior to treatment. As long as blood glucose is consistently maintained between 70 and 100 mg/dl, most children appear to lead fairly normal, healthy lives, with normal growth and development. In general, patients tolerate fasting better after completing adolescence. One of our adult patients can now fast for over eight hours without developing significant hypoglycemia (25).

As more patients are moving into adult life, close evaluation for the development of hepatic adenomas, complications because of hyperlipidemia, and renal disease is essential. We strongly feel that the occurrence of many of these problems may be related to intermittent, suboptimal control of an adequate glucose level, and we cannot overemphasize the need for close follow-up of these patients.

TYPE II GLYCOGEN STORAGE DISEASE

Type II glycogen storage disease (GSD-II) is a lysosomal storage disorder that is due to a deficiency of acid α-glucosidase (35, 69). The disease is inherited in a autosomal recessive manner and is clinically heterogeneous. Three types have been recognized, infantile, juvenile, and adult, based on the age of onset and the severity of symptoms. In the infantile form, symptoms become manifest during the first months of life, with weakness, hypotonia, respiratory difficulties, and cardiac failure usually resulting in death by one to two years of age despite all therapeutic interventions. In the late onset juvenile and adult types, skeletal muscle weakness is usually the only clinical symptom, with resultant respiratory failure being the major cause of death (35, 36, 72).

The severity of symptoms in GSD-II correlates closely with the level of residual α-glucosidase activity and the extent of lysosomal storage of glycogen (36, 61, 72). This storage is due to an inability to degrade lysosomal glycogen to glucose in the absence of α-glucosidase. In the infantile form, the muscle

weakness has been attributed to a disruption of muscle fibers by this excessive lysosomal accumulation of glycogen (32, 45, 77). In the juvenile and adult types, the pathogenesis of the weakness is less clear because morphological changes may be minimal (61, 77). An additional factor, increased net muscle catabolism, may play a role in the development of the myopathy in these patients. In GSD-II both a high rate of muscle turnover and increased use of muscle proteins as a source of energy have been documented (82). These findings have prompted the adoption of high protein diets in treating this disorder. A number of studies have shown that diets providing 30–47% of total calories as protein resulted in significant improvement in muscle strength in juvenile or adult type GSD-II (48, 60, 77, 82).

A group of five adults with acid glucosidase deficiency were treated with a diet containing 16–22% protein for six months (83). A decrease in protein degradation was noted, but no improvement in strength occurred. Possibly, a higher protein intake for longer periods may have had a clinical effect.

High protein diets result in increased levels of branched-chain amino acids (BCAA) (77). These BCAA are the principal amino acids involved in muscle protein synthesis and utilization. Mobarhan et al supplemented a normal diet with an enteral formula containing high levels of BCAA (Travesorb Hepatic®) in an adult with GSD-II (62). Approximately 36% of the patient's total daily caloric intake of 2700 kcal was supplied by the enteral formula. This diet resulted in a significant increase in muscle strength, comparable to that seen with high-protein diets. In addition, higher postprandial concentrations of BCAA were found after the enteral feedings when compared to a high protein meal. As large quantities of food rich in BCAA (fruits, vegetables, meats, dairy products) must be ingested to be beneficial (and maintain adequate total protein intake), the use of an enteral supplement would appear logical. In addition, the use of a liquid supplement is particularly useful in the extremely weak or ventilator-dependent patient. Other enteral formulas containing high levels of BCAA include Hepatic Aid II®, Vivonex TEN®, Stresskin®, and Transverse-Aid HBC®.

TYPE III GLYCOGEN STORAGE DISEASE

Type III glycogen storage disease (GSD-III) is an autosomal recessive disorder that is due to a deficiency of debranching enzyme (amylo-1,6-glucosidase) activity in a number of cells including liver, muscle, leukocyte, erythrocyte, and fibroblast (36, 47). The purified enzyme consists of a single polypeptide chain with two separate catalytic activities: an α-1,4-glucan transferase and an α-glucosidase. A striking enzymic variability is found among patients regarding overall debrancher activity in various tissues and the activities of the transfer and hydrolytic enzymes. On this basis, GSD-III patients have been

divided into eight subtypes (a–h). An absence of enzyme activity in both liver and muscle (GSD-IIIa) accounts for over 75% of the cases (63).

Clinically, GSD-III has many similarities to GSD-I with both conditions manifesting hypoglycemia, hepatomegaly, and growth retardation in early life (22, 36). The clinical course in GSD-III is generally much milder than that of GSD-I, and severe hypoglycemia is not a problem except with prolonged fasting. Serum levels of transaminases are consistently moderately elevated (300 to 600 IU; normal 40 IU), although some patients show elevations of 900–2000 IU, thus indicating varying degrees of hepatocellular damage (22). Patients with GSD-III usually have evidence of hepatic fibrosis but do not necessarily progress to cirrhosis and liver failure. Hug has found several patients with combined defects in phosphorylase and phosphorylase kinase. These patients are generally more severely affected and tend to develop cirrhosis (46). The actual frequency of cirrhosis in GSD-III will obviously require both accurate determination of specific enzyme deficiencies and long-term follow-up.

Lipid levels in serum are variably elevated and to some extent seem to be related to the individual tendency toward fasting hypoglycemia. Uric acid levels are generally normal, but rare patients (usually those with muscle involvement) reportedly have slight elevations. Serum levels of creatinine kinase are elevated in virtually all patients with muscle involvement even prior to or in the absence of clinical weakness.

In addition to hepatic involvement, a number of patients with GSD-III have muscle weakness and some patients may develop a progressive myopathy (36, 63). Low serum levels of branched-chain amino acids have been found in GSD-III and have been considered indicators of increased muscle protein turnover. Excessive gluconcogenesis, as evidenced by low levels of glucogenic enzymes such as alanine, may impose a drain on muscle amino acids and be partly responsible for the muscle wasting reported in isolated cases (64). Glycogen may also accumulate in the heart, and moderate cardiomegaly with nonspecific electrocardiographic and echocardiographic changes may occur (36). However, significant cardiac problems are rare.

The development of hypoglycemia after prolonged fasting may occur in GSD-III patients with liver involvement during infancy and early childhood. This problem may be managed with continuous nocturnal infusions and frequent daytime feedings, as in GSD-I. Treatment of older patients with GSD-III remains investigative and should be restricted to those who have obvious muscle involvement, progressive fibrotic changes in the liver, or both. Current investigative trials combine the technique of nocturnal feeding with known responses to protein and amino acids.

In GSD-III (with muscle involvement) increased dietary protein may be beneficial not only by providing amino acids as substrate for gluconeogenesis

but also for muscle protein synthesis and, possibly, as an alternate fuel for muscle metabolism (64). Slonim and co-workers treated a patient with a high protein diet (25% of total calories) during the day and continuous nasogastric infusions of a high protein formula at night with a resultant improvement in growth and muscle strength (77). More recently, in a patient with only hepatic involvement, Borowitz & Greene found that growth, transaminase levels, and blood glucose values were more positively influenced by a high starch diet with a standard protein intake (6). These studies are encouraging, but more extensive follow-up evaluation over a longer period of time is needed. In addition, the necessity of an accurate diagnosis in regard to specific organ involvement is obviously essential for planning therapy and assessing response.

TYPE IV GLYCOGEN STORAGE DISEASE

Type IV glycogen storage disease (GSD-IV), a rare form of glycogenosis, is due to a deficiency of branching enzyme activity (α-1,4-glucan-6-glycosyl transferase) in the liver as well as in cultured skin fibroblasts and other tissues including the brain, heart, and skeletal muscle (2, 8, 36). A deficiency of this enzyme results in the formation and accumulation of an insoluble and irritating form of glycogen, with longer outer and inner chains and few branch points. The lack of solubility of the abnormal glycogen has been thought to induce a foreign body reaction that results in cellular damage and death (36, 47).

These infants appear normal at birth with an insidious onset of symptoms during the first year of life. The disorder is usually diagnosed because of hepatosplenomegaly, abdominal distention, hypotonia, nonspecific gastrointestinal symptoms, and failure to thrive. Patients who live beyond infancy develop cirrhosis, and death is usually due to chronic hepatic failure by three to four years of age (22, 36).

In these infants, other than supportive nutritional management for terminal cirrhosis, no specific treatment appears to be beneficial. Liver transplantation is currently the recommended form of treatment for these patients. The results of liver transplantation in seven patients with GSD-IV have recently been published and are quite encouraging (76).

TYPE V GLYCOGEN STORAGE DISEASE

Type V glycogen storage disease (GSD-V), a rare form of glycogenosis is due to a deficiency in the activity of myophosphorylase in skeletal muscle (67). As a result of this deficiency, muscle glycogenolysis is impeded, and the utilization of glycogen as an immediate source of fuel is lost. Patients with GSD-V have exercise-induced muscle cramping and weakness usually beginning in childhood with progression to myopathy during adult life in some patients (36).

In normal individuals, resting or minimally active muscle derives the majority of its energy from the oxidation of fatty acids. If muscular contraction is intense or prolonged, the oxygen supply becomes insufficient for the aerobic oxidation of these fatty acids. When this occurs, glucose units are promptly released from muscle glycogen by the phosphorylase enzyme and fed into the glycolytic pathway. The transition from an aerobic to anaerobic metabolism is detectable by the elevation of serum lactate (36, 67).

An absence of myophosphorylase activity results in an inability to release glucose from skeletal muscle glycogen stores. The energy normally produced by anaerobic glycolysis is thus unavailable to these patients during periods of increased muscle activity, with resultant muscle cramping and weakness during exercise. This disruption in energy supply results in alteration of muscle membrane, which is reflected by the presence of muscle enzymes (creatinine kinase) and myoglobin in the blood. Myoglobin is also present in the urine, and renal failure may occur in up to seven percent of patients (37). The lack of a rise in blood lactate during ischemic work in GSD-V is a useful clinical manifestation of impaired anaerobic muscle metabolism. This finding is not unique to GSD-V but is found in deficiencies of any of the glycolytic enzymes. Likewise, excessive degradation of the adenine nucleotide pool with resultant elevation in blood ammonia and uric acid may occur in GSD-V and other myopathic enzyme deficiency states (36, 80). The actual determination of enzyme activity is therefore essential to distinguish between these disorders.

Therapy for GSD-V consists of (*i*) Avoidance of strenuous exercise and (*ii*) dietary attempts to fuel skeletal muscle anaerobic metabolism. Exercise limitation is often impractical and undesirable in young, otherwise healthy individuals. In addition, over 20% of these patients will develop a myopathy in later life despite exercise avoidance (36, 78). Dietary supplementation with glucose or fat in an attempt to substitute for glycogen consumption as an energy source has been unsuccessful (56, 78, 84). The use of high protein diets has yielded conflicting results in GSD-V and is briefly reviewed.

In normal subjects glucose (glycogen) and fatty acids are the main fuel during muscle activity while amino acids contribute minimally to energy production. However, exercise is associated with increased protein degradation and decreased protein synthesis (5). In addition, normal subjects lose alanine from muscle during exercise, whereas patients with GSD-V have a net uptake of alanine by muscle (86). This suggests that amino acids might play a role in energy production in this disorder. Slonim & Goans demonstrated a marked uptake of leucine and isoleucine by muscle in a patient with GSD-V. Administration of a high protein diet (25–30% of total caloric intake) resulted in improved endurance but not muscle strength (78). It was postulated that a metabolic adaptation allows patients with GSD-V to utilize amino acids as a direct source of muscle energy. The use of the BCAA as an alternate muscle fuel would be expected to decrease the availability of these substances for

muscle protein synthesis, leading to net muscle catabolism and progressive muscle weakness and wasting. High protein diets and/or supplementation with BCAA might provide additional fuel and substrate for muscle protein synthesis in these patients.

A recent study using magnetic resonance spectroscopy demonstrated improved strength and endurance after 6 weeks of a high protein diet (29% of total caloric intake) in a patient with GSD-V (52). Interestingly, an intravenous infusion of amino acids did not improve muscle kinetics. This finding suggests that intracellular protein degradation is the main source of amino acids for energy production in these patients.

A number of other investigators have found no significant improvement in muscle function after either high protein diets or supplementation with BCAA (4, 38, 55). These conflicting results emphasize the need for larger cooperative studies so that the effects of heterogenity and/or other sources of variation can be observed by the same investigators and analyzed with statistical rigor.

GLYCOGEN STORAGE DISEASES VI-X

The remaining glycogen storage diseases (GSD-VI-X) are summarized in Table 1. In most of these disorders specific dietary therapy is not required. Possible exceptions are the types with muscle involvement (GSD's VII, IXb, and IXc). Based on experience with the other muscle glycogenoses, a trial with a high protein diet may be of some benefit.

Literature Cited

1. Ambruso, D. R., McCabe, E. R. B., Anderson, D., Beaudet, M. D., Ballas, L. M., et al. 1985. Infectious and bleeding complications in patients with glycogenosis Ib. *Am. J. Dis. Child.* 139:691–97
2. Anderson, D. H. 1952. Studies on glycogen disease with report of a case in which glycogen was abnormal. In *Carbohydrate Metabolism,* ed. V. A. Ajjar, pp. 28–42. Baltimore: Johns Hopkins Press
3. Anderson, J. W., Gustafon, N. J., Bryant, C. A., Tiotyen-Clark, J. 1987. Dietary fiber and diabetes: A comprehensive review and practical application *J. Am. Diet. Assoc.* 87: 1190–97
4. Argov, Z., Bank, W. J., Maris, J., Chance, B. 1987. Muscle energy metabolism in McArdle's syndrome by in vivo phosphorus magnetic resonance spectroscopy. *Neurology* 37:1720–24
5. Bier, D. M., Young, V. R. 1983. Exercise and blood pressure: nutritional considerations. *Ann. Int. Med.* 98:864–69
6. Borowitz, S. M., Greene, H. L. 1987. Cornstarch therapy in a patient with type III glycogen storage disease. *J. Pediatr. Gastroenterol. Nutr.* 6:631–34
7. Brosh, S., Boer, P., Jupfer, J., deVries, A., Sperling, O. 1976. De nove synthesis of purine nucleotides in human peripheral blood leukocytes: excessive activity of the pathway and hypoxanthine quanine phosphoribosyl transferase deficiency. *J. Clin. Invest.* 58: 289–300
8. Brown, B. I., Brow, D. 1966. Lack of an α-1,4-glucan: α-1,4-glucon-6-glycosyl transferase in a case of type IV glycogenosis. *Proc. Natl. Acad. Sci. USA* 56:725–29
9. Burchell, A., Waddell, I. D. 1991. The molecular basis of the hepatic microsomal glucose-6-phosphatase system. *Biochim. Biophys. Acta* 1092:129–37

10. Chen, Y. T., Coleman, R. A., Scheinman, J. I., Kolbeck, P. C., Sidbury, J. B. 1988. Renal disease in type I glycogen storage disease. *N. Engl. J. Med.* 318:7–11
11. Chen, Y. T., Cornblath, M., Sidbury, J. B. 1984. Cornstarch therapy in type I glycogen-storage disease. *N. Engl. J. Med.* 310:171–75
12. Cohen, J. L., Vinik, A., Falker, J., Fox, I. H. 1985. Hyperuricemia in glycogen storage disease type I. Contributions by hypoglycemia and hyperglucagonemia to increased urate production. *J. Clin. Invest.* 75:251–57
13. Coleman, J. E. 1974. Metabolic interrelationships between carbohydrate, lipids, and proteins. In *Diseases of Metabolism*, ed. P. K. Bondy, L. E. Rosenberg, pp. 107–220. Philadelphia: Saunders.
14. Corby, D. G., Putnam, C. W., Greene, H. L. 1974. Impaired platelet function in glucose-6-phosphatase deficiency. *J. Pediatr.* 85:71–76
15. Cori, G. T., Cori, D. F. 1952. Glucose-6-phosphatase of the liver in glycogen storage disease. *J. Biol. Chem.* 199:661–70
16. Czapek, E. E., Deykin, D., Salzman, E. W. 1973. Platelet dysfunction in glycogen storage disease type I. *Blood* 41:235–47
17. Fernandes, J., Berger, R., Smit, G. P. A. 1984. Lactate as a cerebral metabolic fuel for glucose-6-phosphatase deficient children. *Pediatr. Res.* 18:335–39
18. Fine, R. N., Strauss, J., Donnell, G. N. 1966. Hyperuricemia in glycogen storage disease type I. *Am. J. Dis. Child.* 112:572–76
19. Folk, C. C., Greene, H. L. 1984. Dietary Management of Type I glycogen storage disease. *J. Am. Diet. Assoc.* 84:3, 293–301
20. Forget, P. P., Fernandes, J., Begemann, P. H. 1974. Triglyceride clearing in glycogen storage disease. *Pediatr. Res.* 8:114–19
21. Friedman, Z. V. I., Seyberth, H., Lamberth, E. L., Oates, J. 1978. Decreased prostagladin E turnover in infants with essential fatty acid deficiency. *Pediatr. Res.* 12:711–14
22. Ghishan, F. K., Greene, H. L. 1990. Inborn errors of metabolism that lead to permanent liver injury. In *Hepatology A Textbook of Liver Disease,* ed. D. Zakim. T. D. Boyer, pp. 1300–48. Philadelphia: Saunders. 2nd ed.
23. Gilchrist, G. S., Fine, R. N., Donnell, G. N. 1968. The hemostatic defect in glycogen storage disease type I. *Acta Paediatr. Scand.* 57:205–8
24. Greene, H. L., Helinek, G. L., Folk, C. C., Courtney, M. E., Thompson, S., et al. 1981. Nasogastric tube feeding at home: A method of adjunctive nutritional support of malnourished patients. *Am. J. Clin. Nutr.* 34:1131
25. Greene, H. L., Parker, P. H., Slonim, A. E., Burr, I. M. 1981. Resolution of the need for continuous nocturnal feeding in a patient with severe type I glycogen storage disease. *J. Pediatr.* 99:602
26. Greene, M. L., Seegmiller, J. E. 1969. Elevated erythrocyte phosphoribosylphrophosphate in x-linked uric aciduria: importance of PRPP concentration in regulation of human purine biosynthesis. *J. Clin. Invest.* 48:32a
27. Greene, H. L., Slonim, A. E., Burr, I. M. 1979. Type I glycogen storage disease: a metabolic basis for advances in treatment. *Adv. Pediatr.* 26:63–92
28. Greene, H. L., Slonim, A. E., Burr, I. M., Moran, J. R. 1980. Type I glycogen storage disease: five years of management with nocturnal intragastric feeding. *J. Pediatr.* 96:590–95
29. Greene, H. L., Slonim, A. E., O'Neill, J. A., Burr, I. M. 1976. Continuous nocturnal intragastric feeding for the management of type I glycogen storage disease. *N. Engl. J. Med.* 294:423
30. Greene, H. L., Swift, L. L., Knapp, H. R. 1991. Hyperlipidemia and fatty acid composition in patients treated for type IA glycogen storage disease. *J. Pediatr.* 119:398–403
31. Greene, H. L., Wilson, F. A., Hefferan, P., Terry, A. B., Moran, J. R., et al. 1978. ATP depletion, a possible role in the pathogenesis of hyperuricemia in glycogen storage disease type I. *J. Clin. Invest.* 62:321–28
32. Griffin, J. L. 1984. Infantile acid maltase deficiency. I. Muscle fiber destruction after lysosomal rupture. *Virchows Arch. B* 45:123–35
33. Hardinge, M. G., Swarner, J. B., Crooks, H. 1965. Carbohydrates in foods. *J. Am. Diet. Assoc.* 46:197–214
34. Havel, R. J., Balasse, E. O., Williams, H. E., Kane, J. P., Segel, N. 1969. Splanchnic metabolism in von Gierke's disease (glycogenosis type I). *Trans. Assoc. Am. Physicians* 82:305–23
35. Hers, H. G. 1963. α -Glucosidase deficiency in generalized glycogen-storage disease (Pompe's disease). *Biochem. J.* 86:11–16
36. Hers, H. G., Van Hoof, F., Barsy, T. 1989. Glycogen storage diseases.

In *The Metabolic Basis of Inherited Disease,* ed. C. R. Scriver, A. L. Beaudet, W. S. Sly, D. Valle, pp. 425–52. New York: McGraw-Hill. 6th ed.

37. Holmes, E. W., McDonald, J. A., McCord, J. M., Wyngaarden, J. B., Kelly, W. N. 1973. Human glutamine phosphoribosyl-pyrophosphate amidotransferase: kinetic and regulatory properties. *J. Biol. Chem.* 248:143–50
38. Hopewell, R., Yeater, R., Ullrich, I. 1989. The effect of three test meals on exercise tolerance of an individual with McArdle's disease. *J. Am. Coll. Nutr.* 7:485–89
39. Howell, R. R. 1965. The interrelationship of glycogen storage disease and gout. *Arthritis Rheum.* 8:780–86
40. Howell, R. R. 1968. Hyperuricemia in childhood. *Fed. Proc.* 27:1078–89
41. Howell, R. R. 1978. The glycogen storage diseases. In *The Metabolic Basis of Inherited Disease,* ed. J. B. Stanbury, J. B. Wyngaarden, D. S. Fredrickson, pp. 137–59. New York: McGraw-Hill. 4th ed.
42. Howell, R. R., Ashton, D. M., Wyngaarden, J. B. 1962. Glucose-6-phosphatase deficiency glycogen storage disease. Studies on the interrelationships of carbohydrate, lipid, and purine abnormalities. *Pediatrics* 29: 553–62
43. Howell, R. R., Stevenson, R. E., Ben-Menachem, Y., Phyliky, R. L., Berry, D. H. 1976. Hepatic adenomata with type-1 glycogen storage disease. *J. Am. Med. Assoc.* 236:1481–84
44. Huelsmann, W. C., Eijkenboom, W. H. M., Koster, J. F., Fernandes, J. 1970. Glucose-6-phosphatase deficiency and hyperlipidemia. *Clin. Chim. Acta* 3:775–82
45. Hudgson, P., Fulthorpe, J. J. 1975. The pathology of type II skeletal muscle glycogenosis. *J. Pathol.* 116:139–47
46. Hug, G. 1976. Glycogen storage disease. *Birth Defects* 12:145–75
47. Illingworth, B., Cori, G. T. 1952. Structure of glycogens and amylopectins. III. Normal and abnormal glycogen. *J. Biol. Chem.* 199:653–60
48. Issacs, H., Savage, N., Badenhorst, M., Whistler, T. 1986. Acid maltase deficiency: a case study and review of the pathophysiological changes and proposed therapeutic measures. *J. Neurol. Neurosurg. Psychiatry* 49:1011–18
49. Jakovcic, S., Khachadurian, A. K., Hsia, D. Y. Y. 1966. The hyperlidemia in glycogen storage disease. *J. Lab. Clin. Med.* 68:769–79
50. Jakovcic, S., Sorensen, L. B. 1967. Studies of uric acid metabolism in glycogen storage disease associated with gouty arthritis. *Arthritis Rheum.* 10:129–34
51. Jenkins, D. J. A., Wolever, T. M. S., Nineham, R., Bacon, S., Smith, R., Hockaday, T. D. 1979. Dietary fiber and diabetic therapy: a progressive effect with time. *Adv. Exp. Med. Biol.* 119:275–79
52. Jensen, K. E., Jakobsen, J., Thomsen, C., Henriksen, O. 1990. Improved energy kinetics following high protein diet on McArdle's Syndrome. A31P magnetic resonance spectroscopy study. *Acta Neurol. Scand.* 81:499–503
53. Kalhan, S. C., Gilfillan, C., Tsering, K., Savin, S. M. 1982. Glucose production in type I glycogen storage disease. *J. Pediatr.* 101:159
54. Kelley, W. N., Rosenbloom, F. M., Seegmiller, J. E., Howell, R. R. 1968. Excessive production of uric acid in type I glycogen storage disease. *J. Pediatr.* 72:488–96
55. Kushner, R. F., Berman, S. A. 1990. Are high protein diets effective in McArdle's disease? *Arch. Neurol.* 47: 383–84
56. Layzer, R. B. 1985. McArdles disease in the 1980's. *N. Engl. J. Med.* 6:370–71
57. Levy, E., Letarte, J., Lepage, G., Thibault, L., Roy, C. C. 1987. Plasma and lipoprotein fatty acid composition in glycogen storage disease type I. *Lipids* 22:381–85
58. Levy, E., Thibault, L. A., Roy, C. C., Bendayan, M., Lepage, G., et al. 1988. Circulating lipids and lipoproteins in glycogen storage disease type I with nocturnal intragastric feedings. *J. Lipid. Res.* 29:215–26
59. Limmer, J., Fleig, W. E., Leupold, D., Bittner, R., Ditschuneit, H., et al. 1988. Hepatocellular carcinoma in type I glycogen storage disease. *Hepatology* 8:531–37
60. Margolis, M. L., Hill, A. R. 1986. Acid maltase deficiency in an adult. *Annu. Rev. Respir. Dis.* 134:328–31
61. Mehler, M., DiMauro, S. 1977. Residual acid maltase activity in late onset acid maltase deficiency. *Neurology* 27: 178–84
62. Mobarhan, S., Pintozzi, R. L., Damle, P., Friedman, H. 1990. Treatment of acid maltase deficiency with a diet high in branched chain amino acids. *J. Parent. Enterol. Nutr.* 14:210–12
63. Moses, S. 1990. Muscle glycogenosis. *J. Inherit. Metab. Dis.* 13:452–65
64. Moses, S. W. 1990. Pathophysiology

and dietary treatment of the glycogen storage diseases. *J. Pediatr. Gastroenterol. Nutr.* 11:155–74

65. Ockerman, P. A. 1965. Glucose, glycerol, and free fatty acids in glycogen storage disease type I blood levels in the fasting and nonfasting state: effect of glucose and adrenalin administration. *Clin. Chim. Acta* 12:370–78
66. Parker, P., Burr, I., Slonim, A. E., Ghishan, F. K., Greene, H. L. 1981. Regression of hepatic adenoma in type Ia glycogen storage disease with dietary therapy. *Gastroenterology* 81:534–36
67. Pearson, C. M., Rimer, D. G., Mommaerts, W. F. H. M. 1961. A metabolic myopathy due to absence of muscle phosphorylase. *Am. J. Med.* 30:602–10
68. Poe, R., Snover, D. C. 1988. Adenomas in glycogen storage disease type I. *Am. J. Surg. Pathol.* 12:477
69. Pompe, J. C. 1932. Over idopatische hypertophie van het hart. *Ned. Tijdschr. Geneeskd.* 76:304–14
70. Powell, R. C., Wentworth, S. M., Brandt, I. K. 1981. Endogenous glucose production in type I glycogen storage disease. *Metabolism* 30:433–50
71. Ravio, K. O., Seegmiller, J. E. 1973. Role of glutamine in purine synthesis and in quanine nucleotide formation in normal fibroblasts and in fibroblasts deficient in hypoxanthine phosphoribosyl transferase activity. *Biochim. Biophys. Acta* 299:282–92
72. Reuser, A. J. J., Kroos, M., Willemsen, R., Swallow, D., Tager, J. M., et al. 1987. Clinical diversity in glycogenosis type II: biosynthesis and in situ localization of acid d-glucosidase in mutant fibroblasts. *J. Clin. Invest.* 79:1689–99
73. Roe, T. F., Kogut, M. D. 1977. The pathogenesis of hyperuricemia in glycogen storage disease, type I. *Pediatr. Res.* 11:664–69
74. Roe, T. F., Kogut, M. D., Buckingham, B. A. 1979. Hepatic tumors in glycogen-storage disease type I. *Pediatr. Res.* 13:931–35
75. Sadeghi-Nejad, A., Presente, E., Binkiewiez, A., Senior, B. 1974. Studies in type I glycogenosis of the liver: the genesis and disposition of lactate. *J. Pediatr.* 85:49–55
76. Selley, R., Starzl, T. E., Yunis, E., Brown, B. I., Kendall, R. S., et al. 1991. Liver transplantation for type IV glycogen storage disease. *N. Engl. J. Med.* 324:32–42
77. Slonim, A. E., Coleman, R. A., McElligot, M. A., Najjar, J., Hirschhorn, I. 1983. Improvement of muscle function by high-protein therapy. *Neurology* 33:34–38
78. Slonim, A. E., Goans, P. J. 1985. Myopathy in McArdle's syndrome: improvement with a high protein diet. *N. Engl. J. Med.* 312:355–59
79. Slonim, A. E., Lacy, W. W., Terry, A. B., Greene, H. L., Burr, I. M. 1979. Nocturnal intragastric therapy in type I glycogen storage disease: effect on hormonal and amino acid metabolism. *Metabolism* 28:707–15
80. Sutton, J. R., Toews, C. J., Ward, G. R., Fox, R. H. 1980. Purine metabolism during strenuous exercise in man. *Metabolism* 29:254–60
81. Tsallkion, E., Simmons, P., Gerich, J. E., Howard, C., Haymond, M. W. 1984. Glucose production and utilization in children with glycogen storage disease type I. *Am. J. Physiol.* 247: E513–19
82. Umpleby, A. M., Trend, P. St. J., Chubb, D., Conaglen, J. V., Williams, C. D., et al. 1989. The effect of high protein diet on leucine and alanine turnover in acid maltase deficiency. *J. Neurol. Neurosurg. Psychiatry* 52:954–61
83. Umpleby, A. M., Wiles, C. M., Trend, P. StJ., Scobie, I. N., Macleod, A. F., et al. 1987. Protein turnover in acid maltase deficiency before and after treatment with a high protein diet. *J. Neurol Neurosurg. Psychiatry* 50:587–92
84. Viskokper, R. J., Wolf, E., Chaco, J., Katz, R., Chowers, I. 1975. McArdle's syndrome: the reaction to a fat rich diet. *Am. J. Med. Sci.* 269:217–21
85. von Gierke, E. 1929. Hepatonephromagalia glykogenia (Glykogenspeicherkrankheiten Leber und Niepen). *Biete. Pathol. Anat.* 82:497–508
86. Wahren, J., Felig, P., Havel, R. J., Jorfeldt, L., Pernow, B., et al. 1973. Amino acid metabolism in McArdle's syndrome. *N. Engl. J. Med.* 288:744–77
87. Wolfsdorf, J. I., Plotkin, R. A., Crigler, J. F. 1990. Continuous glucose for treatment of patients with type I glycogen-storage disease: comparison of the effects of dextrose and uncooked cornstarch on biochemical variables. *Am. J. Clin. Nutr.* 52:1043–50
88. Yudkoff, M., Nissim, I., Stanley, C., Baker, L., Segal, S. 1984. Glycogen storage disease: effect of glucose infusion on [15N]glycine kinetics and nitrogen metabolism. *J. Pediatr. Gastroenterol. Nutr.* 3:81–88