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Hepatic glycogen storage disorders: what have we learned in recent years?

Patricie Burda[a,c] *and Michel Hochuli*[b,c]

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Glycogen storage disorders (GSDs) are inborn errors of metabolism with abnormal storage or utilization of glycogen. The present review focuses on recent advances in hepatic GSD types I, III and VI/IX, with emphasis on clinical aspects and treatment.

Recent findings
Evidence accumulates that poor metabolic control is a risk factor for the development of long-term complications, such as liver adenomas, low bone density/osteoporosis, and kidney disease in GSD I. However, mechanisms leading to these complications remain poorly understood and are being investigated. Molecular causes underlying neutropenia and neutrophil dysfunction in GSD I have been elucidated. Case series provide new insights into the natural course and outcome of GSD types VI and IX. For GSD III, a high protein/fat diet has been reported to improve (cardio)myopathy, but the beneficial effect of this dietary concept on muscle and liver disease manifestations needs to be further established in prospective studies.

Summary
Although further knowledge has been gained regarding pathophysiology, disease course, treatment, and complications of hepatic GSDs, more controlled prospective studies are needed to assess effects of different dietary and medical treatment options on long-term outcome and quality of life.

Keywords
complications, glycogen storage disease, hypoglycemia, liver, metabolic control, outcome

INTRODUCTION

Glycogen is the storage form of glucose in mammalian cells and is most abundant in liver and muscle. In liver, glycogen serves as a source of glucose to maintain normal blood glucose between meals. In muscle, glycogen provides glucose for glycolysis and ATP production, the energy for active contracting muscle cells. Glycogen storage disorders (GSDs) are a group of inborn errors of metabolism with abnormal storage or utilization of glycogen, resulting from various genetic deficiencies of enzymes for glycogen breakdown or synthesis, or from mutations of proteins regulating glycogen metabolism. Different types of GSDs are classified on the basis of the deficient enzymes and affected tissues [1]. Hypoglycemia and hepatomegaly are the cardinal presenting features of GSDs affecting the liver. Exercise intolerance with muscle pain and rhabdomyolysis, or muscle weakness and cardiomyopathy are signs of GSDs affecting muscles. Long-term complications are frequent with GSDs, often constituting the main disease burden over time.

In recent years, additional knowledge has been gained about the pathophysiology, disease course, treatment, and complications associated with GSDs. The present review focuses on advances in hepatic GSD types I, III, and VI/IX (Table 1), with emphasis on clinical aspects relevant for treatment and follow-up of patients.

GLYCOGEN STORAGE DISEASE TYPE I

GSD type I (GSD I) occurs in two subtypes resulting from deficiencies of glucose-6-phosphatase (G6Pase-α) or the glucose-6-phosphate transporter (G6PT). G6PT translocates G6P into the endoplasmic

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KEY POINTS

- GSDs are multisystemic disorders and have to be managed in a cross-disciplinary way.
- Poor metabolic control is a risk factor for the development of long-term complications.
- Hepatic complications such as liver fibrosis/cirrhosis can also occur in GSD IX subtypes previously considered as benign.
- A high protein/fat diet reduced in carbohydrates has been reported to improve (cardio)myopathy in GSD III.
- More prospective studies are needed to assess the effects of different dietary and medical treatment options on long-term outcome and quality of life.

reticulum, wherein the phosphatase reaction catalyzed by G6Pase-α takes place [1,2▪▪]. The subtype GSD Ia (G6Pase-α deficiency) is most prevalent. About 20% of GSD I patients are classified as GSD Ib (G6PT deficiency) [2▪▪]. The primary metabolic abnormality of both subtypes of GSD I is fasting hypoglycemia, because glucose cannot be formed from glucose-6-phosphate that is produced either via gluconeogenesis or glycogenolysis (Fig. 1). Other associated metabolic abnormalities are lactic acidosis, marked hypertriglyceridemia, hypercholesterolemia, and hyperuricemia, depending on metabolic control [1].

Dietary treatment is the cornerstone of GSD I therapy. A regular carbohydrate intake is necessary to avoid hypoglycemia and to achieve good metabolic control. Glucose requirements generally decrease with age, and adults typically have a longer fasting tolerance. Traditional approaches to maintain normoglycemia during night-time are continuous tube feeding, or ingestion of slowly digested carbohydrates at bedtime, usually uncooked corn starch (UCCS). A modified form of corn starch (Glycosade) with a different content of amylopectin and resistant starch can prolong euglycemia overnight in some patients [3]. A systematic review and metaanalysis of different dietary approaches to maintain normoglycemia in GSD I has shown that both (intermittent) UCCS and continuous feeding of dextrose safely maintain normal blood glucose during nighttime, and physical development was similar for both treatment options [4▪]. During daytime, intermittent administration of UCCS prevented hypoglycemia in children more effectively than intermittent dextrose alone or an UCCS–dextrose mixture. However, conclusions of this meta-analysis were based on four relatively small trials, with limitations such as the heterogeneity in duration of treatment and follow-up, patient age, and disease severity, as well as lack of information on additional dietary factors [5]. In practice, large intraindividual and interindividual differences in glucose response to diet are common, although only small differences in digestibility were observed between different brands of UCCS and modified corn starch in a standardized in-vitro gastrointestinal model [6]. However, many additional factors will influence the kinetics of glucose release *in vivo*. The optimal mode to deliver carbohydrates remains to be tailored to the individual patient, with the goal to achieve best possible metabolic control. Special care has to be taken to avoid excessive energy intake and ensure a balanced diet with adequate macronutrient and micronutrient intake [7].

Despite optimal treatment, many GSD I patients will develop complications such as liver adenomas, chronic kidney disease, urolithiasis, low bone density/osteoporosis, and anemia. Neutropenia and inflammatory bowel disease (IBD) are characteristic features of GSD Ib (Table 1) [8]. Recently, guidelines regarding diagnosis and management of GSD I have been released [9▪▪].

Development of liver adenomas is frequent, with a risk of rupture and bleeding, local compression, and progression into malignancy (hepatocellular carcinoma). Evidence is accumulating that poor metabolic control may be a risk factor for adenoma formation. High triglyceride levels adversely affected adenoma-free survival [10]. In line with this observation, regression of adenoma size was documented in some patients once better metabolic control with lower triglycerides was achieved [11].

However, liver adenomas can also develop in patients with good and stable metabolic control, and the biology of adenoma formation in GSD I still is incompletely understood. Commonly, hepatic adenomas are classified into four molecular subtypes. Molecular characterization of resected adenomas revealed a distinct profile of molecular subtypes in GSD I compared with sporadic adenomas [12▪▪], with a higher proportion of adenomas activated for β-catenin (CTBNN1 mutation), a subtype associated with a higher risk of malignant transformation. To date, no specific imaging procedure or biochemical test can reliably exclude malignant transformation of liver adenomas, often resulting in management dilemmas in case of size progression of liver adenomas. Specific circulating micro-RNAs in plasma may constitute a new approach to monitor adenoma formation in the future, although the additional value of micro-RNAs to discriminate benign adenomas from areas of malignant transformation will need to be demonstrated [13].

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Table 1. Overview of hepatic GSDs presented in this review

GSD type Enzyme affected/gene	Presentation[a]	Typical associated complications
GSD I (Van Gierke) **Ia:** Glc-6-phosphatase α (G6PC) **Ib:** Glc-6-phosphate transporter (G6PT, *SLC37A4)*	Hepatic	GSD Ia and Ib: Liver adenomas – hepatocellular carcinoma Chronic kidney disease with renal failure Osteopenia–Osteoporosis Nephrolithiasis Gout Anemia, platelet dysfunction GSD Ib: Neutropenia, impaired neutrophil function Inflammatory bowel disease
GSD IIIa/b (Cori, Forbes) Debranching enzyme/*AGL*	GSD IIIa[b]: Hepatic and myopathic GSD IIIb: Hepatic	Liver fibrosis – Cirrhosis – Liver failure Liver adenomas – Hepatocellular carcinoma Progressive myopathy Concentric hypertrophic cardiomyopathy Cardiac dysfunction–Arrhythmias
GSD VI Glycogen Phosphorylase/*PYGL*	Hepatic (generally mild)[c]	See type IX, adults often asymptomatic
GSD IX **IXa** (X-linked liver glycogenosis; XLG) Phosphorylase b kinase/α-subunit (*PHKA2)* **IXb** Phosphorylase b kinase/β-subunit (*PHKB)*[d] **IXc** Phosphorylase b kinase/γ-subunit (*PHKG2)*	Hepatic (very variable, often mild)	Clinical and biochemical features often improve with age Liver fibrosis–Cirrhosis (mostly IXc, *PHKG2*)

GSD, Glycogen storage disorder. With the exception of GSD IXa (X-linked inheritance) all GSDs listed are inherited in a autosomal recessive manner.
[a]Cardinal symptoms of a hepatic presentation: hypoglycemia and hepatomegaly. Cardinal symptoms of a myopathic presentation: progressive muscle weakness and/or cardiomyopathy.
[b]Hepatic symptoms usually predominant in children, myopathy with increasing age.
[c]Cardiomyopathy has been observed in some cases with GSD VI.
[d]Some degree of (cardio)myopathy may be observed with IXb.

Anemia is highly prevalent in GSD I, and the degree of anemia strongly correlates with the presence of liver adenomas especially in GSD I [14]. Hepcidin production by liver adenomas is likely to contribute to iron refractory anemia due to reduction of intestinal absorption and recycling of iron by macrophages. However, an anemia of chronic disease is often observed without the presence of liver adenomas, although often less severe. Adenoma resection may improve anemia in many patients. In GSD Ib, anemia is also associated with the presence and severity of IBD [14]. Recently, a case series demonstrated that IBD rarely can also be present in patients with GSD Ia [15]. Progressive anemia should prompt an evaluation for the presence of IBD or liver adenomas.

Molecular mechanisms leading to neutropenia and neutrophil dysfunction in GSD Ib are being elucidated [2▪▪]. Deficiency of the G6PT/G6Pase-β complex in neutrophils impairs energy homeostasis and function, and activates the hypoxia-inducible factor-1α/peroxisome proliferator-activated receptor-γ pathway leading to impairments in respiratory burst, chemotaxis, and calcium mobilization [16▪▪].

Disturbed bone metabolism with low bone density is a typical feature of GSD I. Recent studies confirmed that low bone density is associated with poorer metabolic control (higher triglycerides and higher blood lactate), poor treatment compliance, and the presence of other long-term complications [17,18▪]. In GSD Ib, reduced bone density correlates with granulocyte colony-stimulating factor (G-CSF) treatment, more specifically the duration of treatment and lower age at initiation of G-CSF treatment [18▪].

Chronic kidney disease is frequent with microalbuminuria as a first sign of glomerular damage. GSD nephropathy can evolve to overt proteinuria and/or renal failure especially in the setting of poor metabolic control. Kidney disease in GSD I is similar to diabetic nephropathy, although the pathogenesis is still unclear. A mouse model with a targeted

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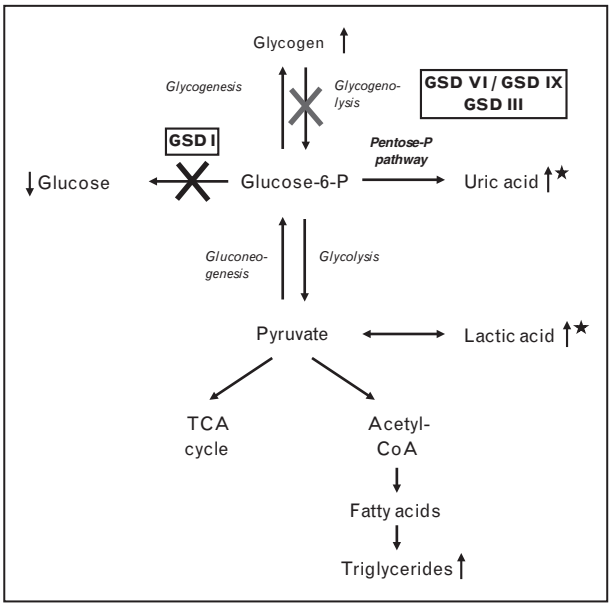

FIGURE 1. Metabolic derangements in liver glycogenoses (glycogen storage disorders). During fasting the liver maintains glucose homeostasis through glycogen breakdown (glycogenolysis) and gluconeogenesis. Dephosphorylation of Glc-6-P to glucose catalyzed by Glc-6-phosphatase is the last step of glucose formation. In glycogen storage disorders type 1 (GSD I) dysfunction of this last step results in hypoglycemia when exogenous carbohydrates are exhausted. Accumulation of Glc-6-P with increased fluxes through the glycolytic and lipogenic pathways is one of the proposed mechanisms for hyperlactatemia and hypertriglyceridemia. In GSD types III, VI and IX, glucose production via glycogenolysis is impaired but gluconeogenesis is functional. (*) denotes metabolic abnormalities specifically related to GSD I.

deletion of kidney G6Pase has been generated and will enable further research to decipher molecular mechanisms underlying renal failure in GSD I [19▪].

Growth retardation with short stature, and/or delayed puberty is often associated with GSD I. Multiple factors may contribute to these problems, but underlying mechanisms are incompletely understood. Despite the frequent occurrence of irregular menses, fertility seems intact with successful pregnancies and good neonatal outcome [20]. There is evidence for hepatic growth hormone resistance in a mouse model [21▪], but the pathophysiology of the typical growth retardation in humans remains to be further investigated.

Quality of life can be impaired in adult patients with GSD I. According to a recent study using the standardized Short Form (36) Health Survey (SF-36) questionnaire, especially patients with GSD type Ib, women, and those with renal complications were more likely to have an impaired quality of life [22▪].

Optimal management and prevention of long-term complications in GSD I remains difficult. Liver transplantation is a therapeutic option for patients with recurrent progressive adenomatosis not amenable to liver resection, or when hepatocellular carcinoma is suspected. Liver transplantation corrects the metabolic abnormality and glucose homeostasis, in exchange with the risk of the procedure and the morbidity of lifelong immunosuppression [23▪▪]. Some long-term problems persist after transplantation, such as chronic kidney disease, and in GSD Ib neutropenia/neutrophil dysfunction and IBD.

Experimental therapies such as delivering deficient G6Pase activity to the liver by gene therapy are being investigated in animal models [24▪,25]. The gradual loss of transgene expression remains a significant challenge in the development of such therapies. Liver stem cell therapy also is being studied as a future therapeutic option [26].

GLYCOGEN STORAGE DISEASE TYPE III

GSD type III (GSD III) is caused by a deficiency of glycogen debrancher enzyme (amylo-1,6-glucosidase) and results in accumulation of 'abnormal' glycogen with short outer chains in various tissues (Table 1) [1,27]. There are two major GSD III subtypes: GSD type IIIa affects both the liver and muscle and accounts for approximately 80% of all GSD III cases, whereas patients with GSD IIIb only have symptoms of liver disease. Great phenotypic diversity is observed with variable severity of the clinical course.

During infancy and early childhood, the hepatic presentation is predominant with hepatomegaly, hypoglycemia, elevated transaminases, and hyperlipidemia. These features often improve with age; however, long-term complications can develop in a significant proportion of patients such as liver fibrosis/cirrhosis with a risk of hepatic carcinoma formation, or rarely hepatic adenomas. Clinically relevant myopathy with slowly progressive muscle weakness typically develops later and may become a predominant feature in adults with GSD IIIa. Exercise tests showed that skeletal muscle symptoms not only are caused by muscle wasting, but may also be related to insufficient energy production due to reduced glycogenolytic capacity [28▪]. Cardiomyopathy can also develop and usually presents with asymptomatic left ventricular hypertrophy, but can progress to hypertrophic cardiomyopathy with decreased left ventricular function and/or arrhythmias [29].

Generally, cognitive impairments have not been associated with GSD III. Recently, cognitive,

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psychopathological, and behavioral profiles were characterized in a small cohort of GSD III patients [30], revealing some psychological and attention deficits. However, a causative role of the metabolic derangement has not been demonstrated.

GSD III management guidelines were published a few years ago [27]. Dietary treatment is the mainstay of therapy. Prevention of hypoglycemia and maintenance of euglycemia is the main focus in early childhood. Hypoglycemia is controlled by frequent carbohydrate meals and a form of continuous carbohydrate supply overnight (e.g., UCCS) [27]. In contrast to GSD I, protein can be used as an additional source for glucose production because gluconeogenesis is functional. In recent years, several reports have been published showing an improvement of (cardio)myopathy following a high protein or protein/fat diet reduced in carbohydrates [31,32▪,33,34]. Such findings highlight the importance of protein in the dietary treatment of GSD III. Sufficient amounts of protein replacing dietary carbohydrates may reduce the accumulation of 'abnormal' short-branched glycogen in affected organs. Whether long-term muscular, cardiac, or even liver complications can be prevented by this dietary approach cannot be answered at present and needs to be further investigated with systematic prospective studies over a longer period [35▪▪].

GLYCOGEN STORAGE DISEASE VI/IX

Glycogen phosphorylase kinase catalyzes the phosphorylation of inactive glycogen phosphorylase converting the phosphorylase to its active form. Subsequently, phosphorylase catalyzes the sequential cleavage of glucosyl units from glycogen to release glucose 1-phosphate. GSD type VI is caused by glycogen phosphorylase deficiency. GSD type IX results from dysfunctional phosphorylase kinase, an enzyme consisting of four subunits. Different GSD IX subtypes are described, depending on the subunit affected [1,36▪▪]. The clinical presentation is very heterogeneous and variable, classically mild with hepatomegaly, elevated transaminases and dyslipidemia, but can also be more severe with short stature, hypoglycemia, and progressive liver disease/cirrhosis (Table 1). Childhood symptoms often improve with age. Mild cardiomyopathy has been observed in GSD VI and GSD IXb [36▪▪]. The most common GSD IX subtype is IXa, due to mutations in the α-subunit of phosphorylase kinase, encoded by the *PHKA2* gene. GSD IXa is likely to be an underdiagnosed cause of ketotic hypoglycemia [37]. The clinical picture of GSD IXa virtually overlaps with GSD type VI, except that inheritance of GSD type IXa is X-linked, whereas GSD VI is an autosomal recessive disorder. Therefore, GSD type VI and IXa mainly are differentiated by molecular genetic investigations. GSD IXc related to mutations in the γ-subunit (*PHKG2*) is associated with a more severe phenotype and a high prevalence of liver fibrosis that can even present with cirrhosis in childhood [38]. The γ-subunit contains the catalytic site of the enzyme that might explain the more severe phenotype. In contrast, GSD IXa classically has been regarded as a benign condition without complications, and treatment has often been considered unnecessary. But case reports are emerging that liver fibrosis/cirrhosis can also develop with GSD IXa [36▪▪,39▪]. In a case series, it was shown that aggressive structured dietary treatment with UCCS and a relatively high protein intake not only resulted in improvement of growth velocity, general well-being and energy, hepatomegaly and biochemical abnormalities, but also regression of sonographic features of fibrosis [39▪].

DIAGNOSIS OF HEPATIC GLYCOGEN STORAGE DISEASES

In the first instance, the diagnosis of hepatic GSDs requires a careful clinical history and examination. Typical laboratory abnormalities help to differentiate between the GSD types (Table 1). Biotinidase activity has been presented as a useful biomarker for hepatic GSDs [40,41]. The definite diagnosis finally is a combination of clinical presentation, specific constellation of biochemical abnormalities, determination of liver enzyme activity (if necessary), and molecular genetic analysis. With the advances in next-generation sequencing (NGS) technologies, mutation analysis has become a preferred method for diagnosing GSDs [42▪]. The NGS approach is attractive, because a group of candidate genes can be sequenced simultaneously and liver biopsies requiring very careful specimen handling can be avoided. Nevertheless, the detection rate of GSDs is highly dependent on an accurate clinical and laboratory evaluation and novel mutations can be only confirmed as disease causing by measuring the according enzyme activity.

CONCLUSION

A cross-disciplinary approach including intensive dietary treatment to achieve good metabolic control, and adequate medical (or surgical) therapy of associated problems and complications is essential to reduce morbidity, mortality, and improve the quality of life of patients with GSDs. However, despite optimal treatment and compliance, long-term complications often develop and mechanisms

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remain poorly understood. Controlled prospective clinical trials to evaluate treatment options are scarce, which is a general problem in the field of rare diseases. Recommendations often are based on clinical experience and expert opinion. Prospective studies are needed to assess effects of different dietary and medical treatment options on long-term outcome and quality of life. In future, proteomic and metabolomic techniques might identify new biomarkers useful for patient follow-up and monitoring of treatment efficacy.

New experimental treatment approaches, such as hepatic gene therapy or liver stem cell therapy are being investigated in animal models. However, risks and additional benefits over established treatment options in humans remain to be studied.

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Conflicts of interest

There are no conflicts of interest.

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