

AN OVERVIEW OF CURRENT DIETARY OPTIONS FOR PATIENTS WITH GLYCOGEN STORAGE DISEASES: IMPACT ON GUT MICROBIOTA AND OXY-INFLAMMATORY STATUS

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ABSTRACT – Glycogen storage diseases (GSDs) are complex hereditary metabolic diseases regarding glycogen metabolism involving different organs and systems. Patients with GSDs require a multidisciplinary approach to therapy, from diagnosis and throughout life. Improving the life course prognosis of patients has shifted the primary objective of management from exclusively avoiding hypoglycemia and guaranteeing survival to the prevention of long-term complications through personalized dietary approaches based on the individual's needs. Nevertheless, the special diet followed by patients may promote gut dysbiosis. The alteration of gut-microbiota composition may probably lead to clinical manifestations linked to an oxy-inflammatory status due to the bidirectional communication through the gut-liver axis. These considerations lay the foundations for a more comprehensive clinical study to define possible therapeutic interventions that can modulate the composition of gut microbiota and reduce oxy-inflammation.

KEYWORDS: Glycogen storage diseases, Dysbiosis, Gut microbiota, Gut-brain axis, Diet, Oxy-inflammatory status.

INTRODUCTION

Glycogen storage diseases (GSDs) are a group of rare inherited disorders caused by a defect in the enzymatic reactions involved in glycogen metabolism, affecting its synthesis, breakdown, utilization in glycolysis, and even lysosomal metabolism¹. GSDs can be classified into three types, according to the type of tissue involved and related clinical phenotype: hepatic, muscular, and hepatic and muscular GSDs (Table 1)¹⁻³.

The clinical presentation of hepatic GSDs consists of hepatomegaly, failure to thrive and hypoglycemia⁴. Hypoglycemia is secondary to the impaired conversion of glycogen to glucose during short fasting⁵. Nutritional therapy remains the cornerstone of treatment for hepatic GSDs, improving the outcome for these disorders⁶. The primary goals of dietary management of GSDs are to maintain blood glucose levels through dietary-administered carbohydrates (CHO), ensuring a metabolic balance that allows normal growth and prevents long-term complications⁴. The treatment varies according to the metabolic pathway involved, ranging from complex intensive feeding routines with overnight tube feeding to simpler treatments of fasting avoidance and management of illness episodes⁷.

Table 1. Glycogen storage diseases classification.

GSD type	Enzyme or protein deficiency	Mode of inheritance	Main presentation
GSD 0	Hepatic glycogen synthase	Autosomal recessive	Hepatic
GSD Ia	Glucose-6-phosphatase- α catalytic subunit	Autosomal recessive	Hepatic
GSD Ib	Glucose-6-phosphate transporter	Autosomal Recessive	Hepatic
GSD II	α -1,4 glucosidase	Autosomal recessive	Muscular
GSD IIb	LAMP-2 protein	X-linked dominant	Muscular
GSD III	Debranching Enzyme	Autosomal recessive	Hepatic and Muscular
GSD IV	Glycogen branching enzyme	Autosomal recessive	Hepatic and Muscular
GSD V	Glycogen phosphorylase (muscle)	Autosomal recessive	Muscular
GSD VI	Glycogen Phosphorylase (liver)	Autosomal recessive	Hepatic
GSD VII	Phosphofructokinase	Autosomal recessive	Muscular
GSD IXa	Phosphorylase Kinase β subunit (liver)	X-linked recessive	Hepatic
GSD IXb	Phosphorylase Kinase β subunit	Autosomal recessive	Hepatic
GSD IXc	Phosphorylase kinase β subunit	Autosomal recessive	Hepatic
GSD IXd	Phosphorylase kinase β (muscle)	X-linked recessive	Muscular
GSD XI	GLUT2 transporter	Autosomal recessive	Hepatic

Source: Chen and Weinstein 2016³. Adapted with permission from IOS Press.

Gut microbiota is defined as a complex community of microorganisms living in the gastrointestinal (GI) tract of humans⁸. Diet has been identified as one of the major factors influencing its composition and function⁹. In addition to providing nourishment, the intestinal microbiota performs various tasks, such as producing short-chain fatty acids (SCFAs), interacting with the mucosal immune system, and providing colonization resistance against pathogens¹⁰. Eubiosis condition is essential for an individual's health since gut microbiota has a high metabolic activity and systemically influences several metabolic processes. Numerous benefits are produced for both the host and the gut bacteria by their interaction¹⁰; an imbalance of it appears to be related to certain pathologies, such as inflammatory bowel diseases (IBDs), cardiovascular diseases, allergies and metabolic disorders¹⁰. In addition to mediating the influence of gut microbiota in GI homeostasis, the gut-liver axis is a great bidirectional communication system mediated by portal vein, biliary tract, and systemic mediators, through which the liver and the intestines converse and influence one another, both in healthy and pathological conditions⁹. The metabolites generated by the host and intestinal bioreactor do not stop at the intestinal wall but enter the circulation through the portal vein and impact the liver and other organs and systems. Dysbiosis has been shown to promote oxidative stress and affect the host's inflammatory and immune systems. Increased amounts of lipopolysaccharide (LPS) are present in the bloodstream due to compromised gut barrier integrity⁹. Increased inflammation at a systemic level underlies the pathogenesis of some diseases, also described as complications of patients with glycogenosis (e.g., obesity, insulin resistance, non-alcoholic fatty liver disease (NAFLD), also known as non-communicable diseases); a condition of local inflammation may also be related to IBD¹⁰. The inflammatory condition frequently linked to metabolic syndrome was named "metabolic endotoxemia" by Cani et al¹¹. Metabolic endotoxemia initiates obesity and insulin resistance¹¹. Obese individuals with insulin resistance have been shown to have higher circulating levels of LPS. Insufficient production of SCFAs by the gut microbiota may also result in elevated intestinal permeability, exacerbating metabolic endotoxemia and lower-grade inflammation⁹.

The purpose of this review is to provide an overview of dietary treatments available and indicated for the various types of glycogenosis, to illustrate which dysbiotic characteristics have been found in studies conducted so far in these patients, and to attempt to illustrate and further explore the relationship between diet, dysbiosis, and the oxy-inflammatory state. These investigations' ultimate goal is to define the potential treatment approaches capable of ameliorating gut microbiota composition.

MATERIALS AND METHODS

For this work, the authors chose a narrative review of the literature, with the aim of providing an overall synthesis of the arguments, with interpretation and criticism, while maintaining methodological rigor¹². Indeed, the authors independently searched via PubMed/MEDLINE database the English-language articles published in the last 10 years (2014–2024) based on the following research strategies:

1. (((glycogenesis) OR (glycogen storage disease) AND ((gut microbiota) OR (microbiota) AND (y_10[Filter]))). Number of documents = 13
2. (((glycogenesis) OR (glycogen storage disease) AND ((oxidative stress) OR (inflammation) AND (y_10[Filter]))). Number of documents = 123
3. (((glycogenesis) OR (glycogen storage disease) AND ((diet) OR (dietetic) OR (nutrition) OR (dietary treatment) AND (y_10[Filter]))). Number of documents = 371

We included original systematic reviews, narrative reviews, research articles, guidelines, case reports in our analysis. From a total of 507 articles, 352 were excluded based on titles and abstracts. The authors reviewed the full texts available focusing on GSD, selecting articles of interest to this review. In addition, they included relevant articles published before 2014. As a result, 57 articles were selected (Figure 1).

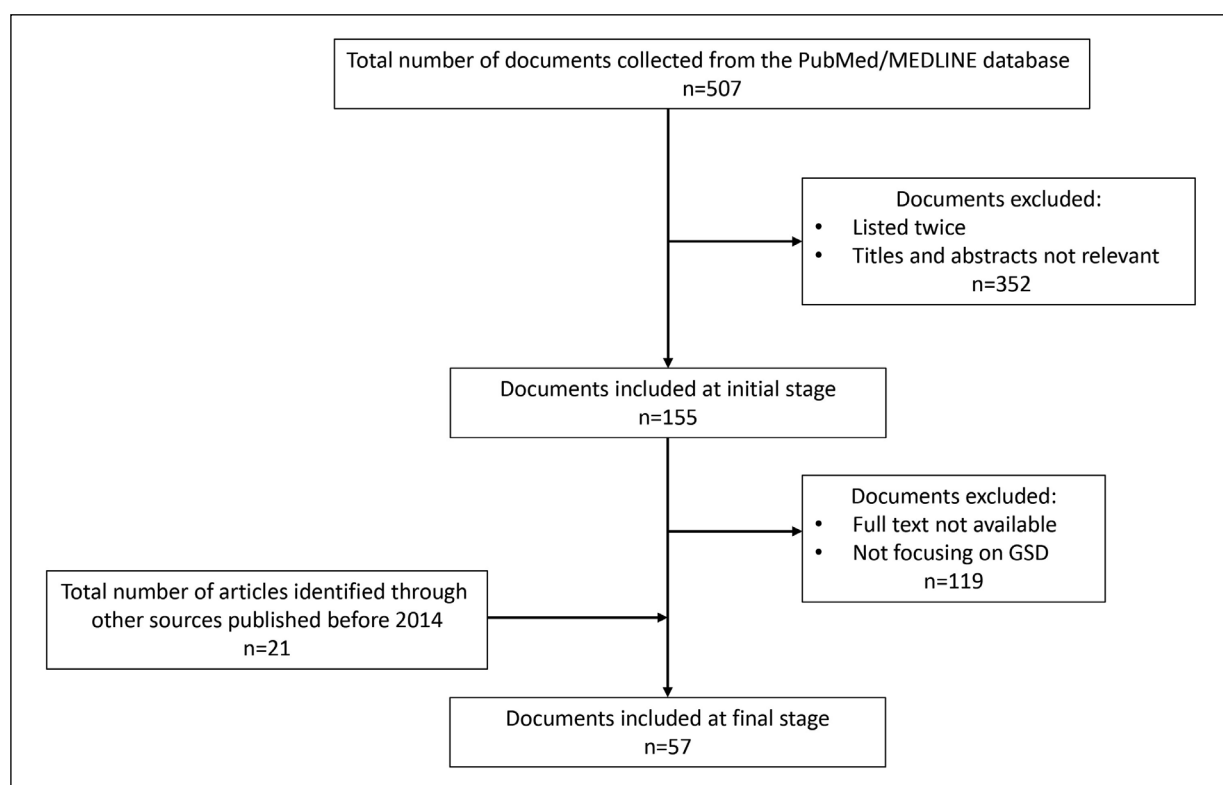


Figure 1. Flow chart of the literature search and selection process.

RESULTS

GSD and dietary treatment

GSD type I

GSD type I (GSD I), also referred to as von Gierke disease, is the most frequent and severe of the hepatic forms of GSDs^{13,14}. While GSD Ia is due to defects of the catalytic subunit of the glucose-6-phosphatase enzyme, GSD Ib is caused by glucose-6-phosphate transporter³. Glucose production is inadequate if either enzyme is deficient, as the glucose formation from glycogenolysis and gluconeogenesis is defective. Both forms are characterized by symptoms, such as hypoglycemia, failure to thrive, developmental de-

lay and hepatomegaly. Therefore, the aim of the dietary treatment for GSD I is to prevent hypoglycemia by administering frequent meals, uncooked cornstarch (UCCS) therapy after 9 months of age, or even enteral nutrition via nasogastric tube feedings^{15,16}. Infants and children are given a frequent supply of glucose day and night. In the dietary treatment of GSD I, UCCS is normally introduced between 9 and 12 months of age to maintain blood glucose concentration in the desirable range¹⁷. As a slowly digested starch, UCCS provides a sustained source of glucose that lasts longer than any other food source. Additionally, the subtype GSD Ib is typically associated with chronic neutropenia and impaired neutrophil function, with increased susceptibility to recurrent bacterial infections, oral and intestinal mucosal ulcerations and a high risk of chronic IBD similar histopathologically to Crohn's disease (CD)¹⁸. However, a few cases of IBD with GI symptoms, such as recurrent abdominal pain, bloating and changes in stool form or frequency, have been recently reported in the subtype GSD Ia as well^{10,19}. Long-term complications are reported in both types, mainly involving:

- the liver, with the development of hepatocellular adenomas (HCA) and hepatocellular carcinomas (HCC);
- the kidney, evolving into renal insufficiency;
- growth delay;
- joints, with gout manifestations;
- and bones, with low bone mineral density and osteopenia²⁰.

Good metabolic control is essential to delay the onset and severity of these complications. The latest international guidelines for GSD I provide precise indications regarding the qualitative and quantitative composition of diet therapy during the pediatric, adolescent and adult age of affected patients¹⁷. Specifically, to maintain normoglycemia, the recommended macronutrient composition of the diet shows an increased CHO content compared with the normal population. However, the total daily energy intake should be similar: the diet typically provides 60%–70% energy from CHO, 20–25% from fat and 10–15% from protein²¹. However, maintaining a normal energy intake and non-overfeeding intake of complex CHO is important, as the risk of hyperinsulinemia, insulin resistance, obesity, and nutrient deficiency is a well-documented problem in some patients with GSD I¹⁷. As growth improves fasting tolerance in children on intensive dietary treatment, glucose requirements decrease with age and post-puberty glucose therapy can generally be given less frequently. It is important to ensure that only the required amount of CHO is administered, as excessive CHO intake induces peripheral body fat storage due to glycogen overload and hyperlipidemia. The administration of glucose, as well as of UCCS, should be personalized, based on the patient's age and needs, while monitoring glycemic and metabolic control to avoid both overtreatment and undertreatment¹⁷.

The monosaccharides fructose and galactose cannot be converted into glucose in patients with GSD I. Therefore, their food sources must be avoided or severely limited in the diet²¹. Patients with GSD I should also receive sugar-free multivitamin/mineral, calcium and vitamin D supplements to meet the Dietary Reference Intake (DRI) recommendations for the individual's age²¹.

GSD type III

In GSD type III (GSD III), glycogen is no longer completely degraded due to the deficiency of the glycogen debranching enzyme. Consequently, this leads to impaired glucose availability and abnormal intracellular accumulation of limited dextrin in the involved tissues, with frequent hypoglycemia and both hepatic and cardiac/skeletal muscle symptoms²². Two main clinical subtypes of GSD III are described: GSD IIIa (85% of patients) affects the liver and cardiac/skeletal muscle, while GSD IIIb (15% of patients) involves only the liver^{23,24}. Clinically, children usually show hepatomegaly (due to both glycogen and fat accumulation), ketotic hypoglycemia, growth delay, markedly elevated blood transaminase levels, and hyperlipidemia (triglycerides and cholesterol)²⁵. In patients with GSD IIIa, cardiac manifestations and skeletal myopathy may occur with increasing age. Hypertrophic cardiomyopathy can frequently manifest with varying severity and progression of symptoms^{26,27}. Skeletal myopathy develops as weakness and wasting and progresses gradually, becoming much more problematic in adulthood, with increased serum creatine kinase²⁵. Liver symptoms improve with age; therefore, hypoglycemia is a less frequent problem. Functionally, patients with GSD III present with defective glycogenolysis, but gluconeogenesis is preserved with a greater fasting tolerance than in GSD I^{7,22,28}. Guidelines for the diagnosis and management of GSD III were published in 2010²², indicating as the classical dietary treatment the provision of frequent meals with high CHO intake throughout the day, together with UCCS supplements to maintain

euglycemia in young children^{1,22,28}. Infants may need more frequent diurnal meals and continuous nighttime feedings in severe cases⁷. Contrary to GSD I, as gluconeogenesis is still intact, there is no benefit to limiting fructose and galactose¹. Apart from the CHO substrates, the preservation of gluconeogenesis also requires an increased protein intake²². Specifically, a low-CHO and high-protein diet is recommended in adults, with a progressive increase in protein intake and decrease in CHO starting with older children to limit glycogen storage in both liver and muscles, activate gluconeogenesis from glucogenic amino acids and promote muscle protein synthesis^{29–31}. Fasting tolerance improves as the patient grows, allowing longer fasting windows. Although this regimen can prevent fasting hypoglycemia, it does not prevent liver, cardiac, and muscular complications that may still occur in the long-term follow-up, even in well-controlled patients^{22,32}. Administration of CHO may induce reactive hyperinsulinism, resulting in suppression of lipolysis, ketogenesis, gluconeogenesis, and activation of glycogen synthesis, with a reduction in energy availability for the skeletal muscle and the heart^{28,30,33}. Based on these considerations, several case reports have emphasized the positive effects of dietary lipid modification in the management of various forms of GSDs; specifically in GSD III^{4,34}, it includes high-fat, high-protein and low-CHO diet, modified Atkins diet (MAD)^{28,30,35} with or without medium chain triglyceride³⁶, or Ketogenic diet therapies (KDTs), which are a high-fat, adequate-protein, and low-CHO diet, proposed as a valid alternative to the traditional approach^{5,34,37}. All these specific nutritional treatments aim to improve clinical cardiac and muscular outcomes by favoring both gluconeogenesis activity with a high-protein diet and ATP generation through fatty acid oxidation and utilization of ketone bodies as an alternative fuel to CHO for body needs^{27,32,38}. The KDTs are widely used in drug-resistant epilepsies and some inherited metabolic diseases (IEMs), such as GLUT1 and pyruvate dehydrogenase deficiencies. However, the application in other IEMs has no defined and specific dietary protocols. Valayannopoulos et al³² showed an improvement in cardiomyopathy in a 2-month-old infant with GSD III following a KDT with supplementation of synthetic ketone bodies (D, L-3-hydroxybutyrate). MAD is a more flexible and palatable variant of KDTs, with a 1:1 ratio of fat to CHO and protein, and contains around 65% fat, 25% protein, and 10% CHO without any restriction of calories and fluids^{39,40}. The CHO intake is limited to 10–20 g per day in children and 15–20 g per day in adults. For this reason, it represents a more comfortable dietary approach, considering that it could be followed for a long period²⁷. Brambilla et al²⁷ showed marked improvement in clinical condition and biochemical and echocardiographic findings in two siblings, aged 7 and 5 years, affected from GSD IIIa with severe cardiomyopathy, after 12 months of MAD-like diet (fat 60%, protein 25%, CHO 15%). Another clinical case³⁰ reported a similar result in two 9- and 11-year-old boys with GSD IIIa treated with MAD (10 g CHO per day, protein and fatty acids *ad libitum*). A study by Massimino et al⁴¹ performed a gradual shift from a high-CHO (61% total energy intake), low-fat (18%), high-protein (21%) diet to a low-CHO (32%), high-fat (45%) and high-protein (23%) diet in a 24-year-old GSD IIIa patient with severe myopathy and cardiomyopathy, with good efficacy in reducing muscle damage without worsening cardiometabolic profile after a 2-year follow-up. Dyslipidemia associated with MAD has been well described^{42,43}. Francini-Pesenti et al³⁵ documented a slight increase in triglycerides and low-density lipoprotein (LDL) levels in an adult case with GSD IIIa treated with MAD (fat 60%, protein 25%, CHO 15%). A slight increase in total cholesterol and LDL levels was also observed in three out of six patients with GSD IIIa who followed MAD, as presented by Olgac et al²⁸; only triglycerides slightly increased in one out of two children with GSD IIIa in response to MAD, as described by Mayorandan et al³⁰. However, according to the literature, changes in lipid profile due to MAD do not necessarily lead to increased cardiovascular risk, although low-CHO intake has a favorable effect on lipid profile, affecting total cholesterol and LDL cholesterol, with an impact on atherogenesis^{44,45}. A decrease in plasma atherogenic small LDL and an increase in large LDL has also been shown with CHO dietary restriction^{44,45}.

Other GSDs

GSD types VI and GSD IX present defective glycogenolysis but intact gluconeogenesis like GSD III^{4,7}. Therefore, nutritional therapy in GSD VI and IX has similarities with GSD III, focusing on remediating hypoglycemia with CHO, and simple sugars are not limited⁷. Replacing some CHO with protein may improve growth and reverse myopathy⁴⁶. GSD 0 is associated with less severe hypoglycemia than other GSD types, post-prandial lactic acidosis and fasting ketosis, with normal-sized liver⁴⁷. Dietary treatment consists of UCCS, protein supplementation, and restriction of dietary CHO. Calcium and vitamin D supplementation is also required because of the risk of osteoporosis⁴⁷. GSD XI (Fanconi–Bickel syndrome) is characterized by short stature, hypoglycemia, hepatomegaly, hypophosphatemia rickets, postprandial

hyperglycemia, and proximal renal tubular dysfunction⁴⁸. Diet therapy consists of small doses of UCCS around the clock to prolong euglycemia between meals, elimination of glucose and galactose, and small amounts of fructose to correct acute hypoglycemia⁴⁸. Patients with GSD XI should also receive vitamin D, phosphate, and bicarbonate supplementation^{48,49}.

Gut microbiota composition in GSDs

Intestinal bacteria, which are regarded as endocrine organs, are crucial to human health. Recent research in humans has shown a connection between the emergence of metabolic diseases and gut microbiota dysbiosis¹⁰. In light of the previously reported data and considering the role of diet in influencing the gut microbiota composition, the dietary treatment goal of GSDs should be not only the control of the disease itself but also the promotion of healthy eating habits through personalized interventions, despite the generalities of dietary patterns indicated for the disease⁹. As described, several IEMs, including GSDs, require lifelong special diets with a different nutrient balance from the recommendations for the general population, excluding certain nutrients or compounds or overconsuming others⁵⁰. The different bioavailability of dietary substrates affects the gut microbial composition by promoting the overgrowth of bacteria-linked intestinal inflammation with a different production of microbial metabolites and, consequently, systemic effects on the whole body⁹.

The first study reporting the characteristics of the gut microbiota in GSDs was conducted by Colonetti et al¹⁶ in 2019, in which the gut microbiota composition of 24 patients with hepatic GSDs (I, III and IX) treated with UCCS was compared with that of healthy controls (HCs). Intestinal dysbiosis was observed, associated with a lower fecal microbial diversity; in addition, a higher incidence of IBD and obesity/overweight was found in patients with GSD. At the phyla level, Proteobacteria and Actinobacteria were overrepresented in patients with GSD. At the genus level, low concentration or complete absence of some genera was responsible for the low alpha and beta diversity (*Euryarchaeota*, *Coproccoccus*, *Blautia*, *Anaerostipes*, *Odoribacter*, and *Faecalibacterium* were generally less abundant) instead of *Lactobacillus* and *Escherichia/Shigella* genera, which were predominant¹⁶. Colonetti et al¹⁶ considered nutrition as a critical factor influencing microbiota composition. UCCS overload can lead to a low lumen pH, which is a selective factor for the growth of some bacteria instead of others^{16,51}. Therefore, microbial richness has shown a negative correlation with total CHO¹⁶. Moreover, the lower pH inhibits the growth of fiber-fermenting bacteria and the quantity of SCFAs in the gut¹⁶. The gut inflammatory status in GSDs may be impacted by the decreasing level of SCFAs⁵¹. Ceccarani et al⁵² confirmed the significant low biodiversity in patients with GSD Ia and b, the dramatic increase in *Proteobacteria* phylum, with an increased representation of *Enterobacteriaceae* and *Veillonellaceae* families, and a parallel reduction in other beneficial genera, such as *Faecalibacterium* and *Oscillospira*⁵². *Proteobacteria*, and specifically the *Enterobacteriaceae* family, exhibit pro-inflammatory properties both systemically and locally at the GI mucosa level⁵². LPS have been shown to be associated with low-grade inflammation at systemic levels, and it is expressed on the *Proteobacteria* membrane. Although GSD Ib is genetically predisposed to intestinal bowel inflammation, altered inflammatory markers were also found in patients with GSD Ia, and the enrichment in the relative abundance of *Escherichia coli* affected both types Ia and Ib patients^{16,52}. Therefore, these patients exhibited dysbiosis, probably caused mainly by the dietary modification underlying the treatment of these diseases⁵¹. The exact existing link between dysbiosis and the clinical phenotype of the disease is still unclear, but dysbiosis is found to be associated with obesity and IBD¹⁶.

Gokalp et al⁵¹ observed an altered gut microbiota composition in GSD I, with decreased Firmicutes abundance, especially *Faecalibacterium prausnitzii*, and increased Actinobacteria abundance in patients with GSDs compared with controls. Firmicutes, as well as *F. prausnitzii*, are butyrate bacteria producers⁵¹. A reduced presence of *F. prausnitzii* has been reported in several conditions associated with inflammation; therefore, it could be considered a GI tract inflammation marker suggestive of its involvement in dysbiosis in GSD cases⁵¹.

Gokalp et al⁵¹ found an increased abundance of the phylum *Proteobacteria* and *Actinobacteria* in patients with GSDs than in controls, confirming the previous results. Elevated *Proteobacteria* counts can serve as a reliable indicator of dysbiosis⁵¹. A recent study conducted in China investigated gut microbiota profiles in 22 pediatric patients with hepatic GSDs, specifically GSD Ia, III and IXa. All the patients were treated with UCCS and were compared with HCs; 16S rRNA gene sequencing revealed and confirmed that both richness and diversity were significantly lower in patients with hepatic GSDs than in HCs. The

decrease in abundance of phyla Firmicutes and Bacteroidetes, the *Lachnospiraceae*, *Ruminococcaceae* families, and the *Blautia* and *Faecalibacterium* genera, alongside the increase in the phyla Actinobacteria and Proteobacteria, the *Bifidobacteriaceae*, *Enterobacteriaceae*, *Lactobacillaceae*, *Veillonellaceae*, and *Clostridiaceae* families, and the *Bifidobacterium*, *Escherichia-Shigella*, and *Lactobacillus* genera showed similar characteristics to those reported in previous studies⁵³. Interestingly, the concentration of fecal bile acids (BAs) was also assessed, with a finding of an increased relative abundance of primary BAs alongside a decreased relative abundance of secondary BAs when compared with healthy children⁵³.

BAs are signaling molecules that regulate hepatic glucose gluconeogenesis and glycogen synthesis, lipid metabolism, and intestinal incretin secretion, with implications in various metabolic diseases. The elevated primary BA ratio in the BA pool may cause hyperactivation of farnesoid X receptor (FXR) signaling, as primary BAs are endogenous agonists of FXR in the liver. There is an ongoing debate regarding the precise function of FXR in controlling glucose metabolism. Secondary BAs activate G protein-coupled bile acid receptor 1 (GPBAR1), which may contribute to the prevention of liver damage. In patients with hepatic GSDs, the reduced amounts of secondary BAs may contribute to liver injury by compromising GPBAR1 signaling⁵³.

As for SCFAs, less than six carbons and a straight or branched chain conformation characterize fecal SCFAs and small molecules such as succinate, which are produced by microbial fermentation in the large intestine from food-undigested components in the small intestine. The most prevalent SCFAs in the colon are acetic acid (AA), propionic acid (PA), and butyric acid, accounting for 90–95% of the total. These metabolites influence the host biologically. The pH and available substrates have a major impact on their production⁵⁴. AA, PA, and butanoic acid selectively affect hepatic glucose homeostasis through peroxisome proliferator-activated receptor- γ signaling-mediated effects on gluconeogenesis, suggesting that SCFAs may play a regulatory role in glucose homeostasis⁵³. SCFAs, particularly butyrate, are critical to human intestinal health. Generating luminal butyrate can safeguard the integrity of the intestinal barrier, immune system control, and gut microbiota balance. In the intestinal lumen, butyrate-producing bacteria ferment undigested CHO to create SCFAs. Microbiota and gut are balanced by the acidic lumen produced by butyrate-producing bacteria. Their equilibrium strengthens the immune system, enhances digestion, and positively impacts the gut. Dysbiosis may begin in the presence of an imbalance. Luminal epithelial cells create and absorb more than 90% of the luminal SCFAs formed in the lumen. Colonic epithelial cells experience nutritional insufficiency and atrophy if SCFA levels in the lumen are reduced⁵¹. Additionally, it has been demonstrated that butyrate stimulates the expression of gluconeogenic genes related to propionate regulation of intestinal gluconeogenesis. Furthermore, butyrate can enhance liver glycogen metabolism in mice used as type 2 diabetic models. Children with hepatic GSDs showed lower levels of butanoic acid and PA, which may indicate the relation between the alterations in SCFAs and liver glucose processes⁵³. These results show the intricate relationships between microbial metabolites, liver glucose metabolism, and gut microbiota⁵³. Ceccarani et al⁵² found that fecal acetate and propionate levels in patients with GSDs were significantly increased, albeit these levels were probably less beneficial due to imbalanced bacterial interactions. Colonetti et al⁵⁴ recently delved into the role of these metabolites in intestinal inflammation, in particular formic (FA), AA, lactic (LA), PA, and succinic (SA) acids. An increase in SA and a tendency for FA accumulation was observed. The levels of the bacterial metabolites PA and LA were not different between the patient and control groups, but they reached borderline significance and had an intriguing effect on the microbial structure; the effects of PA and LA on the microbial structure appeared to be significantly enhanced by SA, with statistical significance⁵³. The combination of SA and the metabolites resulted in a larger and statistically significant effect, indicating a major function for SA in the gut environment. Furthermore, SA acts as a precursor for propionate synthesis; however, in the presence of sufficient CHO, the demand for decarboxylate succinate decreases, and this metabolite accumulates in place of propionate. Therefore, the use of UCCS might be related to SA levels. SA is an important metabolite for microbial and host activities, as it enhances inflammation by activating immune cells through a G-protein coupled receptor⁵³. Dysbiosis, patients with IBD, and animal models of intestinal inflammation have all shown elevated levels of SA. Microbial diversity and fecal pH are negatively correlated with increased FA and LA. In addition, FA appears to be higher in inflammatory situations and has been connected to methanogenesis; it is an electron donor with oxygen, and oxygen respiration and formate oxidation are metabolic signals for inflammation-related dysbiosis⁵³. Furthermore, the modality of administering nourishment can influence gut microbiota. Previous studies revealed that tube feeding, commonly used as a treatment strategy for children with GSDs, can disrupt the oral indigenous microbiota⁵⁵, creating a permissive environment for *Clostridioides difficile* infection⁵⁶. Enteral tube feeding has difficulty maintaining adequate fluid intake with possible constipation⁹.

Regarding modification in gut microbiota, no studies are available on patients with GSD III undergoing KDT. However, modifications in the gut microbiota of children with drug-resistant epilepsy after a KDT have been investigated in many studies. The KDT is historically used in drug-resistant epilepsy but also in Alzheimer's disease, depression, and autism. Some neurological disorders are also linked to gut microbiota composition through the gut–brain axis. Significant changes in the taxonomic and functional composition of gut microbiota were found in children after only 3 months of the KDT, confirming the crucial role of the diet on microbiota when compared with healthy parents³⁷. In particular, an increase in the relative abundance of Bacteroidetes and Proteobacteria was observed in children, with a parallel reduction in Actinobacteria and Firmicutes. Functional analysis revealed a decreased carbohydrate metabolism pathway, as expected, given the reduction in carbohydrate intake. *Bifidobacteria* break down complex CHO, which explains the proportional decrease in *Bifidobacteria* and genes related to the metabolism of CHO during KDT³⁷. Moreover, *Bifidobacteria* contribute to GI health through SCFA production. The lower presence of acetate and lactate due to *Bifidobacteria* production increases gut pH, with a major risk of pathogen growth, such as *E. coli*, whose relative abundance was found to be increased in the gut microbiota of children during KDT³⁷. Additionally, a diet high in fat and sugar, such as the Western diets, increases the relative abundances of Proteobacteria, which have been linked to intestinal inflammation and an increased risk of contracting *E. coli*⁵⁷. *E. rectale* was found to be decreased in epilepsy patients before starting KDT, with an impact on the total butyrate synthesis, which has anti-inflammatory activity, together with acetate. This difference was augmented during KDT, with a significant reduction in *E. rectale*, probably due to a direct effect of reduced consumption of complex CHO⁵⁸. This study confirms the known critical function of dietary fibers as sources of energy for gut microorganisms to sustain gut health^{59,60}; it also shows that exclusion or exceedance of some determined nutrients leads to a different bioavailability of substrates for gut bacteria, possibly resulting in an imbalanced composition and different microbial metabolites production with systemic effects throughout the body⁵⁰.

GSD and oxy-inflammatory status

The liver, primarily involved in glucose production and homeostasis maintenance, plays a fundamental role in glucose metabolism pathologies. In GSD I, the hepatic production of glucose is discontinued, leading to hypoglycemia. The dysfunction of hepatocyte metabolism in GSD I can lead to stress in the cell⁶¹ and the development of fatty liver and mitochondrial dysfunctions. An increase in the production of ROS and oxidative stress was observed in other diseases affecting glucose metabolism, such as type 2 diabetes. Cell stress may result in lipid peroxidation, DNA and protein alterations, and ultimately the growth of liver tumors⁶¹. Mouse models provided data regarding stress cells in GSD I, with alterations of mitochondrial structure and mitochondrial apoptosis activation⁶². Moreover, patients with GSD I showed low-grade liver inflammation, although normal transaminase levels in patients reached the target^{63,64}. Liver fibrosis has never been described in patients with GSD I. Furthermore, murine models with GSD Ia receiving gene therapy mediated by recombinant adeno-associated virus showed maintained blood glucose homeostasis and did not develop HCA/HCC^{65,66}. Specifically, the absence of HCA/HCC in adeno associated virus non-tumor-bearing (AAV-NT) mice was correlated with upregulation of hepatic AMPK/SIRT1 and FGF21/b-klotho signaling and down-regulation of STAT3/NFjB-mediated inflammatory and tumorigenic signaling pathways⁶⁷, showing that a decrease in the activity of hepatic G6Pase-a favors a reduction in liver inflammation and tumorigenic response as well. In mice with GSD Ia, a recent study⁶⁸ found that circulating exosomal microRNAs show an altered expression correlated with pathologic liver states.

In liver forms of GSDs, IBD and liver disease are common, and hepatocytes result in being sensitive to gut microbial production of metabolites that can enhance systemic inflammation¹⁶. In the past, the standard treatment consisted of the administration of high quantities of CHO to avoid hypoglycemia, leading to weight gain and hyperinsulinism with insulin resistance¹⁷. In addition, abnormalities in plasma acylcarnitines and urine organic acids found in patients with GSD I could be linked to mitochondrial impairment while oxidative stress could be related to hyperinsulinism and insulin resistance⁶⁹. It was also hypothesized that oxidative stress could be related to the pathogenesis of IBD in GSD⁷⁰.

As previously reported, dysbiosis can promote oxidative stress across the gut–liver axis, influencing the host's inflammatory status and the onset of non-communicable diseases, such as obesity, insulin resistance and NAFLD, as a consequence of “metabolic endotoxemia”¹¹, which is the result of increased intestinal permeability and higher circulating levels of LPS.

Figure 2 shows the interaction among GSDs, diet therapy, gut-microbiota composition and oxy-inflammation, mediated by the gut-liver axis. GSD-specific diets, with a high CHO amount, UCCS overload, use of tube feeding, as well as KDTs may contribute to the pathogenesis of dysbiosis and altered hepatic cell metabolism observed in these patients through gut-liver axis with a local and systemic chronic inflammatory status and the development of long-term complications.

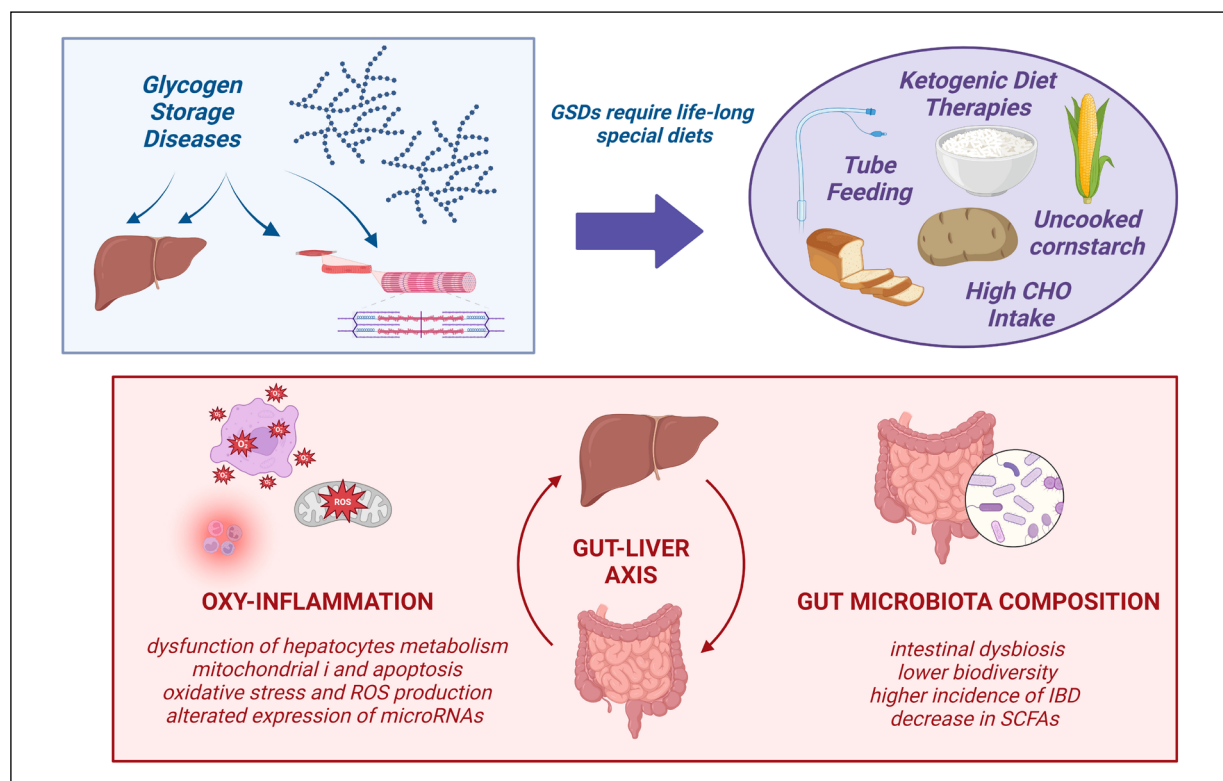


Figure 2. The interaction among GSDs, diet therapy, gut-microbiota composition and oxy-inflammation, mediated by the gut-liver axis. Original figure created with Biorender.com

DISCUSSION

Although GSD management has improved over the past 40 years, with increased survival and aging patients¹⁹, the association between GSD Ib and IBD has been historically described¹⁹. Intestinal inflammation and symptoms are also reported in patients with GSD Ia, such as intermittent diarrhea, which appears to get worse with age; IBD Ia was found in adults with GSD, although not related to the metabolic control of the disease itself¹⁹. The daily consumption of UCCS is the primary factor determining incomplete reabsorption, leading to water retention, severe meteorism, and diarrhea, resembling the symptoms of patients with Crohn-like disease. Therefore, patients with GSD Ia often have idiopathic colon inflammation caused by the ablation and atrophy of intestinal microvilli at the level of the ileum and transverse colon. Several patients with GSD Ia also exhibit endoscopic and/or histological features of CD, with no clear indications of CD or ulcerative colitis. The condition known as Crohn-like IBD is applied to these cases¹⁰. In hepatic GSDs, characterized not only by the avoidance of fasting but also by complex CHO intake (i.e., UCCS), an overload of UCCS is the potential cause of dysbiosis, which in turn could promote inflammation locally in the gut and also systemically⁷¹. A UCCS excess could reduce the pH of the feces and the conversion rate of unabsorbable starch to SCFAs⁷². SCFAs are produced by bacteria, such as *Coprococcus*, *Blautia*, *Anaerostipes*, *Odoribacter*, and *Faecalibacterium*, which were found to be reduced in patients with GSD treated with UCCS compared with controls¹⁶. In 2020, Ceccarani et al⁵² also revealed that UCCS consumption in GSD I was linked to *Veillonella*, *Citrobacter*, and *Akkermansia* genera, and negatively correlated to *Coprococcus* and *Clostridium* genera. Moreover, a reduction in richness and diversity, together with the increase in Proteobacteria and *Escherichia Coli*, was observed. A diet

rich in CHO and fats could also be responsible for the promotion of metabolic stress in the hepatic cells, potentially leading to adverse consequences such as carcinogenesis⁷³. A recent publication⁷⁴ highlighted an accelerated tumor process and transformation into HCC. In GSD Ia mice, this diet worsened the accumulation of lipids and significantly raised the frequency of hepatic tumors and their conversion to HCC, possibly due to the provision of more substrates for glycolysis and lipid synthesis. Lastly, NAFLD is often associated with a lower abundance of *Faecalibacterium*⁷⁵, promoting liver cirrhosis and HCC. The influence of diet on microbiota composition was also demonstrated by changes in microbial composition in relation to the duration of UCCS use. Wang et al⁵³ divided patients with GSD according to the treatment duration, and relative abundances were found to be positively or negatively associated with UCCS intake for <2 years, 2–5 years, and >5 years. Particularly, long-term (>5 years) UCCS treatment was positively associated with the abundance of *Terrisporobacter* and *Sarcina* genera and negatively associated with the abundance of *Megasphaera* genera. Changes in the gut microbiota could have an impact on the development of non-communicable diseases, such as type 2 diabetes, obesity, and metabolic liver diseases; it is interesting to note that changes in the gut microbiota community of hepatic GSDs follow the same pattern in different liver metabolic diseases: higher levels of Proteobacteria, *Enterobacteriaceae*, *Lactobacillus*, *Escherichia*, and lower levels of Firmicutes and *Faecalibacterium*. This suggests that the gut microbiota and host liver metabolism are closely related. For example, the *Prevotella* genera, which was shown to be less prevalent in hepatic GSD children, has been linked to improvements in host glucose metabolism brought about by dietary fiber⁵³.

As nutritional therapy is lifelong, it becomes necessary for a “best patient-personalized clinical practice” to pay attention to possible overtreatment with excessive CHO intake to avoid hypoglycemia and favor macronutrient quality, recommending the consumption of low-glycemic index food and mono- and polyunsaturated fats in order to reduce long-term cardiovascular risk^{9,41}.

In light of a personalized nutrition approach, supplementation with pro-, pre-, or postbiotics (specific biotics) could represent an innovative approach to improving the well-being and overall quality of life of patients with GSDs. To date, the role of specific biotics in GSDs has been poorly investigated. The majority of studies focus on the use of biotics in conditions with similar physiopathological aspects, dietary approach and/or secondary multiorgan involvement, allowing the hypothesis that their application in patients with GSD may represent a potential approach in the management of this disease⁹. In a recent study, Hu et al⁷⁶ investigated the separated and combined effects of *Bifidobacteria* and resveratrol in alleviating obesity and NAFLD. They described that a combination with a prebiotic substrate may improve the effects of probiotics, representing a promising strategy against NAFLD and obesity.

Studies in mice on a high-fat diet have shown that treatment with *Lactobacillus* and *Bifidobacterium* has several beneficial effects on intestinal function by normalizing the dysbiotic microbiota and can increase insulin sensibility⁷⁷.

Probiotics, including *Lactobacillus rhamnosus* and *Lactobacillus reuteri*, have been reported to enhance the immune system, reduce inflammation and intestinal oxidative stress, and restore hepatic damage^{78–85}.

Forsyth et al⁸⁶ observed a significant improvement in alcoholic steatohepatitis and alcohol-induced gut leakiness, with a reduction in markers of intestinal and liver oxidative stress and inflammation and normalization of the gut barrier function, in a rat model of alcohol steatohepatitis daily treated with *Lactobacillus rhamnosus*⁸⁶.

In another study from Werlinger et al⁸⁷, the supplementation of *L. reuteri* MJM60668 to high-fat diet-induced NAFLD mice significantly attenuates alcoholic liver disease interfering with fatty acid metabolic pathways by strongly inhibiting lipogenesis, enhancing fatty acid oxidation, and suppressing inflammation⁸⁷.

In addition, *L. reuteri* changed the gut microbiota population, especially by increasing the proportion of *Akkermansiaceae* in feces, whose low presence in the gut microbiota has been previously associated with metabolic disorders, such as diabetes⁸⁸. This confirms a potential improvement of gut microbiota related to mucus barrier and a decrease in the inflammation of the gut as well as in triglycerides levels⁸⁷.

Carnero-Gregorio et al¹⁰ reported the case of a 36-year-old man with GSD Ia and IBD-like symptoms treated with a mixture of *Lactobacilli*, *Bifidobacteria* and *Streptococcus thermophilus*. At the end of treatment, the patient showed ameliorating GI symptoms, with a reduction in the number of irritable gut episodes. Regular administration of these probiotics led to an increase in Bacteroidetes, *Clostridium leptum* and *Eubacterium* and a decrease in *Enterobacteriaceae* (*Escherichia*, *Klebsiella*, *Proteus*)¹⁰.

Further studies are needed to elucidate whether the improvement in more severe cases of GSDs is mainly due to modeling the intestinal microbiota profile through non-pharmacological nutritional interventions, as in this patient.

CONCLUSIONS

The mandatory lifelong diet therapy and the possible development of long-term complications observed in patients with GSDs, thanks to the clear increase in survival, requires a multidisciplinary and personalized dietary therapeutic approach to GSDs that is configured as a real medium-long term nutritional intervention, focused not only on pathology but also on the entire dietary pattern and its impact on gut microbiota composition. This research may provide insights for the investigation of microbial-targeted therapies, including pre/probiotics in the treatment of hepatic GSD, although the mechanism causing these alterations is unknown and may be mediated by genetic defect, disease state, or diet therapy⁵³.

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