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Review

Update on glycogen storage disease: a brief review of the main disorders

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Abstract

A glycogen storage disease (GSD) is a metabolic disorder caused by a deficiency of an enzyme or transport protein affecting glycogen synthesis, glycogen breakdown, or glucose breakdown, typically in muscles and/or liver cells. Several enzymes are required for the processes of glycogenesis and glycogenolysis. Glycogen storage diseases happen when a person doesn't have one or more of these enzymes. GSD in almost all cases is genetic (In exceptional cases, it can be environmental, like GSD in livestock). Genetic GSD results mainly from inborn error in carbohydrate metabolism, where genetically faulty or malfunctioning enzymes or transport proteins are involved. It has many different types and diagnoses depending upon history, physical examinations and more specifically, blood tests and biopsies for related disturbances and genetic testing wherever mutations are being suspected. It is very important to distinguish the different types so that the patient receives the correct treatment. To even summarize the treatment modalities of the different sub-groups was beyond the scope of this study. We hope that it will elucidate better approaches and techniques amongst collaborative team members from the medical fraternity.

Keywords: Glycogen storage disease, Genetic, Enzyme deficiency, Metabolic disorder.

1. Introduction

Glycogen is a polymer that is branched and glucose is its monomeric unit. The glucose level gets elevated after a meal and stimulates excess glucose storage inside the cytoplasmic glycogen [1]. The highest amount of glycogen (by weight) is contained in the liver, whereas muscles can store about 2% by weight. Nevertheless, since the total muscle mass is greater than liver mass, the total mass of glycogen in the muscle is about twice that of the liver. When needed, the glycogen polymer can be broken down into glucose monomers and utilized for energy production [2]. Many of the enzymes and transporters for these processes are key to the etiology of GSDs. An increasing number of GSDs are being identified, but most are very rare. Traditionally, the GSDs were named after the clinician who first identified the disorder; however, they each have an identified enzyme and gene focus that will be used to refer to these disorders in this article, although the various diseases have their classifications [3]. Glycogen storage diseases (GSDs) are inherited inborn errors of carbohydrate metabolism. Disorders of carbohydrate metabolism that result in abnormal storage of glycogen are classified as GSDs. They are classified numerically in the order of recognition and identification of the enzyme defect causing the disorder. Clinical onset can range from neonatal life to adulthood. Depending on the specific type, GSDs can result from a failure to convert glycogen into energy and/or a toxic glycogen accumulation; however, all result in a failure to use or store glycogen [4]. It has been estimated that this GSD occurs at the rate of 1 in every 20,000 to 43,000 live births; more than eighty percent are caused by types 1, 3 and 9 [5,6]. They are usually classified based on the affected tissues and the deficient enzyme or enzymes. Although the liver and skeletal muscles are most commonly affected, other organs might also be affected [7]. Although GSDs have some similar clinical presentations, the clinical phenotypes are seen in a very wide spectrum. The main hallmark of GSDs is hypoglycemia. One cardinal manifestation is hepatomegaly in almost all, with involvement of the liver except for the GSD-0. Muscle GSDs usually present with muscle cramps/pain, exercise intolerance, muscle weakness and rhabdomyolysis, and

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when heart is involved, cardiomyopathy is seen [8].

1.1. Glycogenesis process

In the beginning, after glucose enters the cell, the glucose molecule is known to interact with the glucokinase enzyme, which adds a group of phosphates to glucose, at the beginning of the glycogenesis process. In the subsequent step of the glycogenesis process, the enzyme phosphoglucomutase assists in moving the phosphate group to the other side of the molecule. Another enzyme involved in this process, UDP-glucose pyrophosphorylase, takes this molecule and converts it to UDPG with the help of UTP. These additions aid in the formation of a chain of molecules, which is essential for the glycogenesis process's subsequent stage. An extremely significant enzyme called glycogenin is essential to the last phase of the glycogenesis process. When the Uridine diphosphate glucose binds to this particular molecule, it usually forms relatively short chains. After about eight of these molecules join to form a chain, more enzymes help the process be completed. Glycogen synthase then receives this chain. The glycogen branching enzyme aids in the development of branches in the chains at the same time (Fig. 1) [9].

1.2. Glycogenolysis process

Glycogenolysis starts when muscle adenyl cyclase and cAMP activities are elevated. Glycogen breakdown is catalyzed by phosphorylase a, which is created when phosphorylase kinase is bound by cAMP and changes into its active state. Glycogenolysis may take place in cytosol or lysosomes. The cytosolic enzyme glycogen phosphorylase catalyzes the synthesis of glucose-1-phosphate from the terminals of glycogen branches by cleaving α-1,4 bonds with inorganic phosphate. Glycolysis is often the result of the conversion of glucose-1-phosphate to glucose-6-phosphate by the enzyme phosphoglucomutase. Lysosomal glycogen is broken down by the lysosome enzyme acid α-glucosidase through a method that depends on autophagy. The enzyme glycogen phosphorylase transfers one of the branches to another chain when it reaches a branch point four glucose residues distant. This creates a new α-1,4 bond and leaves one glucose unit at the branch site, which is subsequently hydrolyzed by α-1,6-glucosidase to provide free glucose (Fig. 2) [10].

1.3. Clinical significance of glycogen metabolism disorders

Clinical Significance of Glycogen Metabolism Disorders: Liver Phosphorylase Deficiency (GSD VI) is due to a lack of liver phosphorylase, McArdle Disease (GSD V) is due to a lack of muscle glycogen phosphorylase, Cori Disease (GSD III) is due to a lack of the debranching enzyme, Andersen Disease (GSD IV) is due to a lack of the branching enzyme, Von Gierke Disease (GSD I) is due to a lack of glucose-6-phosphatase, and Phosphorylase Kinase Deficiency (GSD IX) is due to a lack of phosphorylase kinase [11].

2. Classification of glycogen storage disorders

Glycogen storage disorders (GSDs) are a group of inherited metabolic diseases characterized by the deficiency of enzymes involved in glycogen synthesis or breakdown. These disorders are classified based on the specific enzyme deficiency and the tissues affected, primarily the liver and muscles. For instance, GSD Type I (Von Gierke disease) is the most common form, caused by a deficiency of glucose-6-phosphatase, leading to hepatomegaly and hypoglycemia. GSD Type III (Cori/Forbes disease) involves the debranching enzyme, affecting both liver and muscles. GSD Type V (McArdle disease) affects muscle glycogen phosphorylase, causing exercise intolerance [12-20]. Table 1 shows a comprehensive summary of GSD types, including

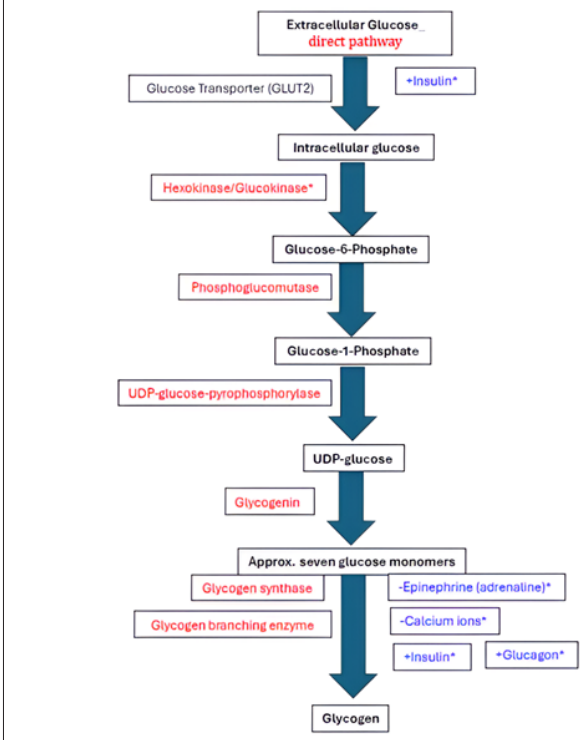

Fig. 1. Brief view of glycogenesis.

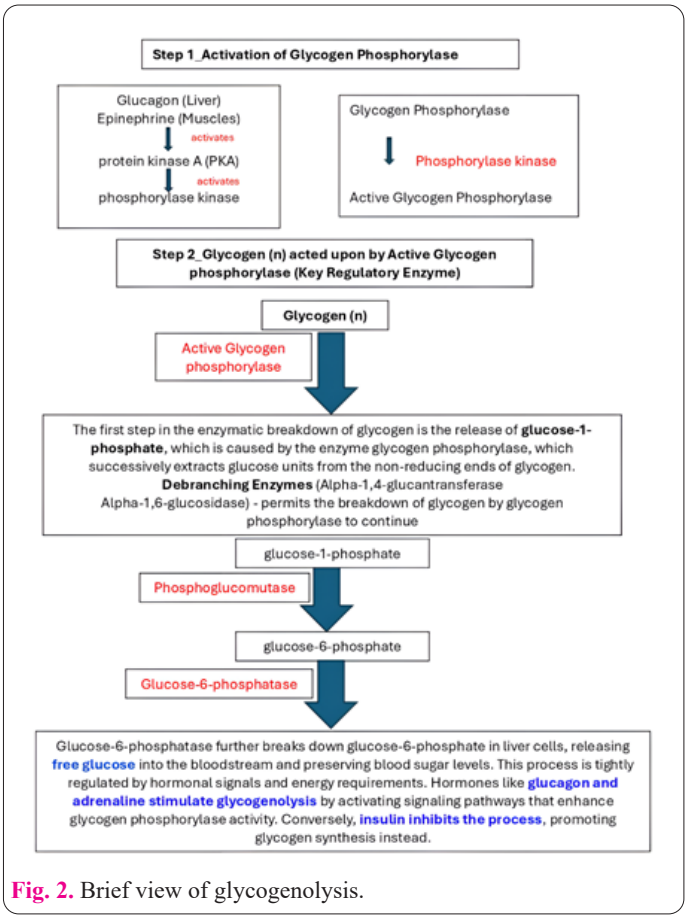

Fig. 2. Brief view of glycogenolysis.

Table 1. Summarizing glycogen storage diseases (GSDs) includes types, associated enzymes, defective genes, chromosomal locations, global incidence, and clinical features.

Type	Name	Defective Enzyme	Defective Gene	Chromosome Location	Clinical Features	References
GSD 0a	Glycogen Synthase Deficiency	Glycogen Synthase	*GYS2* (liver)	12p12.2	Fasting hypoglycemia, fasting ketotic hypoglycemia, hyperalaninemia, no hepatomegaly	12-14
GSD 0b	Glycogen Synthase Deficiency	Glycogen Synthase	*GYS1(muscle)*	19q13.	Muscle pain and weakness, exercise intolerance, cardiomyopathy	13,14
GSD Ia	Von Gierke Disease	Glucose-6-Phosphatase	*G6PC*	17q21.31	Hepatomegaly, hypoglycemia, lactic acidosis, hyperlipidemia, growth retardation	12,20
GSD Ib		Glucose-6-phosphate transporter	*SLC37A4*	11q23.	Hypoglycemia, recurrent infections and neutropenia	19,20
GSD II	Pompe Disease	Acid Alpha-Glucosidase	*GAA*	17q25.3	Cardiomegaly, muscle weakness, respiratory failure, infantile or late-onset forms	16
GSD III	Cori/Forbes Disease	Debranching Enzyme	*AGL*	1p21.2	Hepatomegaly, hypoglycemia, myopathy, cardiomyopathy, growth retardation	16
GSD IV	Andersen Disease	Branching Enzyme	*GBE1*	3p12.2	Hepatosplenomegaly, cirrhosis, failure to thrive, progressive liver failure	17
GSD V	McArdle Disease	Muscle glycogen phosphorylase	*PYGM*	11q13.1	Exercise intolerance, muscle cramps, myoglobinuria, weakness	18
GSD VI	Hers Disease	Liver glycogen phosphorylase	*PYGL*	14q22.1	Hepatomegaly, mild hypoglycemia, growth retardation, hyperlipidemia	16
GSD VII	Tarui Disease	Muscle Phosphofructokinase	*PFKM*	12q13.11	Exercise intolerance, muscle cramps, hemolysis, myoglobinuria	18
GSD IX	IXa	Phosphorylase kinase (α2 subunit)	*PHKA2* (X-linked)	Xp22	Hepatomegaly, growth retardation, mild hypoglycemia, hyperlipidemia; myopathy such as fatigue, cramps, and muscle pain, especially during exercise	20
	IXb	Phosphorylase kinase (β subunit)	*PHKB*	16q12		
	IXc	Phosphorylase kinase (γ subunit)	*PHKG2*	16p11		
	IXd	Phosphorylase kinase (α1 subunit)	*PHKA1*	Xq13		
GSD X	-	Muscle phosphoglycerate mutase	*PGAM2*	7p13	Muscle pains or cramps after strenuous physical exercise. Exercise intolerance. Recurrent episodes of myoglobinuria.	20
GSD XI	Fanconi-Bickel Syndrome	Lactate dehydrogenase A deficiency	*SLC2A2*	3q26.2	Hepatomegaly, renal Fanconi syndrome, growth retardation, fasting hypoglycemia	14
GSD XII	-	Aldolase A	*ALDOA*	16p11	Hemolytic anemia, neurologic abnormalities, and myopathy with exercise intolerance.	20
GSD XIII	-	β-Enolase	*ENO3*	17p13	Exercise intolerance, myalgia, contracture, and generalized muscle weakness after exercise.	20
GSD XV	-	Glycogenin-1	*GYG1*	3q24	Hepatopathy, bifid uvula, malignant hyperthermia, hypogonadotropic hypogonadism, growth retardation, hypoglycemia, myopathy, dilated cardiomyopathy, and cardiac arrest.	20

associated enzymes, defective genes, and clinical features.

3. Glycogen Storage Disease I

3.1. Background

Glycogen Storage Disease I (Von Gierke disease), also known as Hepato-renal glycogenosis, is an inherited enzyme disorder that implicates the pathway of glycogen metabolism (Table 2). It is described by buildup of hepatic andrenal glycogen and lipids leading to liver and renal enlargement [21]. The two common subtypes, Ia and Ib, differ both genetically and clinically, with Glycogen Storage Disease I being the most severe form among liver Glycogen Storage Diseases (Table 1)[22].

3.2. Pathophysiology

This disorder is due to the deficiency of glucose-6-phosphatase. In Glycogen Storage Disease Ia, enzyme disorder is discovered inside endoplasmic reticulum, precisely in the catalytic subunit of the enzyme. Alternatively, type Ib affects transporters that relocate the substrate of the enzyme from and tothe endoplasmic reticulum [23].

3.3. Prevalence

Glycogen Storage Disease I occurs in approximately 1 in 100,000 to 300,000 individuals, with Glycogen Storage Disease Ia being the most common type among those of European ancestry [22]. In the identified articles, the frequency of GSD 1a occurs in 2.41/100,000 newborns in Saudi Arabia [24,25].

3.4. Glycogen storage disease types

3.4.1. Glycogen storage disease type Ia

Glycogen-storage disease type Ia (GSD Ia) designates the true enzyme defect. Glycogen Storage Disease Ia is initiated by G6PC gene variations leading to glucose-6-phosphatase deficit [26]. It was detected that the responsible gene of catalytic unit of glucose-6-phosphatase is found on chromosome 17q21 [27].

3.4.2. Glycogen storage disease type Ib

Glycogen Storage Disease Ib is caused by a deficiency of the glucose-6-phosphate transporter (G6PT) in the membrane of the endoplasmic reticulum, resulting from mutations in the SLC37A4 gene. This deficiency disrupts the transport of glucose-6-phosphate into the endoplasmic reticulum, impairing glucose metabolism and leading to the characteristic neutropenia and neutrophil dysfunction seen in the disease [22,25]. Glycogen storage disease type Ib (GSD-Ib) is an autosomal recessive disorder characterized by hypoglycemia, excessive glycogen accumulation in the liver and kidney, with neutropenia, neutrophil dysfunction, and inflammatory bowel disease. GSD-Ib is caused by a deficiency of glucose-6-phosphate transporter (G6PT) [28].

3.5. Clinical features

Significantly affected newborns present with markedly low levels of blood glucose due to intolerance to fasting. More frequently, neglected patients manifest at 3-4 months' age with enlarged liver, severely low levels of blood glucose, lactic acidosis, with or without convulsions, increased level of uric acid in blood, and increased level of triglycerides in blood.

3.6. Biochemical features

In glycogen storage disease Ia, there is highly elevated serum triglyceride, whereas elevation of phospholipids and cholesterol levels is moderate. Moreover, serum lipoproteins of VLDL and LDL types and apoE concentrations are elevated [22].

3.7. Diagnosis

Hepatic histopathological examination and enzyme evaluations, and/or genetic assay with detection of gene mutation are essential for ultimate diagnosis. Liver enzyme activity examination is only available for glucose-6-phosphatase catalytic function [22].

4. Glycogen storage disease type II (Pompe disease)

4.1. Background

Type II Glycogen storage disease or Pompe Disease is an autosomal recessive disorder, in which the deposit of glycogen occurs in the lysosomes of the muscle tissue [28]. This disease is categorized as early classic or infantile & late onset, which is considered non-classic. The Early onset has a serious presentation & fatal outcome, which would enhance the treatment consideration, though not available except for enzyme replacement therapy. The popular reason for lethality for the early onset is the respiratory insufficiency, which presents at various ages in the later-onset. The other significant reason for the lethality at the beginning of the infantile type is the left outflow ventricular obstruction (Table 3)[29-31].

4.2. Danon disease (formerly GSD-IIb)

It is a Lysosome-associated membrane protein 2

Table 2. Brief description of glycogen storage disease I.

Type of GSD/Another name	*Defective enzyme or other/ Inheritance type*	*Defective gene and location in chromosome*	*Incidence in the world*
Glycogen Storage Disease type Ia/ Von Gierke disease	Glucose-6-phosphatase (G6Pase)/ autosomal recessive	glucose-6-phosphatase gene	prevalence of one in 1,25,000
Glycogen storage disease type Ib	Glucose-6-phosphate transporter/ autosomal recessive	SLC37A4 gene affection	Varies according to ethnicity and region

Table 3. Brief description of glycogen storage disease II.

Type of GSD/Another name	*Defective enzyme or other/ Inheritance type*	*Defective gene and location in chromosome*	*Incidence in the world*
GSD-II/ Pompe's disease	Acid α-glucosidase	GAA gene on chromosome 17q25.3	Varies according to ethnicity and region

(LAMP2), very similar to Pompe disease.

4.2. Pathophysiology

Though the precise mechanism has not been indicated, the accumulation of lysosomal glycogen results in striated muscular impairment in the cells. First, the areas that are affected include the active extremities of voluntary muscles developing into the cardiac muscle & lastly the diaphragm [29]. One of the most detrimental aspects of the pathogenic cascade that occurs in Pompe disease involves the dysregulation of the lysosomal-related signaling pathways [33].

4.3. Differential diagnosis

The differential diagnosis for early-onset disease includes spinal muscular atrophy type 1 (which typically lacks cardiac involvement), Danon disease, and other X-linked disorders. For the late-beginning: limb dystrophy girdle muscular (without infection of the axial muscles), the Duchenne-Becker dystrophy or X-associated inherited. In addition to the Other disorders of glycogen storage that may be involved, the major variation involves the deficiency of hypoglycemia in the GSD2 [30,32].

4.4. Conclusion

Glycogen accumulation is a key factor in many glycogen storage disorders (GSDs), but there are a few significant signs that may prompt physicians to consider these disorders. Both hepatic and muscular symptoms can suggest a GSD. Additional signs include hypoglycemia, elevated serum lactate, and elevated urate levels. Increased creatine kinase and muscular weakness, along with rhabdomyolysis, are also significant indicators. The primary focus of treatment is managing hypoglycemia and other associated symptoms. Supportive therapy is crucial, and enzyme replacement therapy, along with liver or bone marrow transplantation, or recombinant enzyme therapy, offers the most hope for patients with severe phenotypes.

5. Glycogen storage disease type III (Cori's disease or Forbes' disease)

5.1. Background

Glycogen storage disease type III (GSD III) is an autosomal recessive metabolic disorder and inborn error of metabolism (specifically of carbohydrates) characterized by a deficiency in glycogen debranching enzymes [31,34]. It is also known as Cori's disease in honor of the 1947 Nobel laureates Carl Cori and Gerty Cori. Other names include Forbes disease in honor of clinician Gilbert Burnett Forbes (1915–2003), an American physician who further described the features of the disorder, or limited dextrinosis, due to the limited dextrin-like structures in cytosol [35]. Limit dextrin is the remaining polymer produced after hydrolysis of glycogen. Without glycogen debranching enzymes to further convert these branched glycogen polymers to glucose, limited dextrinosis abnormally accumulates in the cytoplasm (Tables 4 and 5)[36].

Table 4. Classification of glycogen storage disease type III.

Type “IIIa”	Affects muscles and liver
Type “IIIb”	Affects liver
Type “IIIc”	Affects liver and muscles
Type “IIId”	Affects liver only

5.2. Pathophysiology

It is a rare disease, having variable clinical severity, and mainly affects the skeletal muscle, heart and liver. Biochemical and clinical marks of glycogen storage disease type three are characteristically like type one with hypoglycemia, hepatomegaly, hyperlipidemia and delayed growth. The presence of splenomegaly and elevated liver transaminases may be observed. Hepatic symptoms and hepatomegaly are primarily characteristic of GSD type III [37]. Involvement of skeletal muscles may occur first, with involvement of liver later. Rarely, there may be involvement of skeletal muscles with no hepatic signs or symptoms. Hepatic symptoms tend to decrease gradually with age and usually resolve after puberty. Cirrhosis of the liver and hepatic cell carcinoma are rare. In adulthood, patients primarily experience progressive muscle weakness and distal muscle wasting. Cardiac involvement is most common in GSD type IIIa. [38,39].

GSD type III has many classifications as the following table (Table 4) shows:

GSD (glycogen storage disease) type III diagnosis is dependent on measuring enzyme levels in muscles and liver. Also, analysis of mutation can be a simple tool to diagnose glycogen storage disease type III. Decreased enzyme levels can also be present in erythrocytes, heart or fibroblasts [40,41]. When liver and muscle enzymes are deficient, glycogen storage disease type III will appear with cardiomyopathy, neuropathy, peripheral myopathy, or cirrhosis of liver in adults or in young neonates. Some complications of “glycogen storage disease” type three can be present as osteoporosis, which is related to poor level of nutrition, hypogonadism and lactic acidosis (Table 5) [42].

6. Glycogen storage disease type IV

6.1. Background

Also called GSD IV (Andersen disease), it is a genetic disorder caused by the accumulation of glycogen, a complex sugar, in the body's cells. The structural abnormalities resulting from the accumulated glycogen affect the function of certain organs and tissues, particularly the liver and muscles. GSD IV is classified into five different subtypes, each of which can be identified by its severity, symptoms, and signs. The diagnosis is based on clinical symptoms and the results of laboratory tests, but molecular analysis is frequently required to differentiate between the different forms. Early detection enables good metabolic control,

Table 5. Brief description of glycogen storage disease III

Type of GSD/Another name	*Defective enzyme or other/ Inheritance type*	*Defective gene and location in chromosome*	*Incidence in the world*
GSD III / Cori's disease or Forbes' disease	Glycogen debranching enzyme	AGL/1p21.2	1 in 100,000

Table 6. Brief description of GSD IV.

Type of GSD/Another name	*Defective enzyme or other/ Inheritance type*	*Defective gene and location in chromosome*	*Incidence in the world*
GSD IV/Andersen's disease	Glycogen branching enzyme (GBE1)	Result of a mutation in the GBE1 gene/3p12.2	1 in 500,000

Table 7. Brief description of GSD V.

Type of GSD/Another name	*Defective enzyme or other/ Inheritance type*	*Defective gene and location in chromosome*	*Incidence in the world*
GSD V /McArdle's disease	Muscle glycogen phosphorylase (PYGM)	Pathogenic autosomal recessive mutations in PYGM gene coding for myophosphorylase/ 11q13.1	1 in 100,000 – 500,000

improving quality of life and prognosis (Table 6) [42,43].

6.2. Inheritance

GSD IV is an autosomal recessive condition. Each affected person's sibling has a 25% chance of developing the disease, a 50% chance of becoming an asymptomatic carrier, and a 25% chance of remaining unaffected and not a carrier. The age of onset and presentation may vary between affected siblings, even though they are anticipated todisplay the same subtype of GSD IV [44].

6.3. Pathophysiology

The two enzymes glycogen synthase (GS), which lengthens the glycogen chain, and glycogen branching enzyme (GBE), which creates new branches, catalyze the process of synthesizing glycogen. Normal glycogen molecules can only be produced when the GS/GBE ratio is correct [44]. GSD IV is brought on by GBE1 gene mutations. The glycogen branching enzyme is made using instructions from the GBE1 gene. An important source of the body's stored energy is glycogen, which is produced by this enzyme. Lack (deficiency) of theglycogen branching enzyme resulting from GBE1 gene mutations is the cause of GSD IV. Glycogen does not develop properly as a result. Polyglucosan bodies, an abnormal form of glycogen, build up in cells and cause harm and eventual cell death.

Although polyglucosan bodies accumulate in cells throughout the body, GSD IV particularly affects the liver and muscle cells. Hepatomegaly results from the buildup of glycogen in the liver, which also impairs its function. Muscle cells' inability to utilize glycogen for energy results in muscle wasting and weakness. Typically, the amount of functional glycogen branching enzyme produced is correlated with the severity of the disorder [45,46].

6.5. Subtypes of GSD type IV

According to the age of onset, GSD type IV has three neuromuscular subtypes (perinatal, congenital, and childhood disease) and two hepatic subtypes (classical progressive and non-progressive hepatic disease) [45].

Glycogen storage disease type IV (GSD IV) has several types, including Hepatic (the classic progressive hepatic type and the non-progressive hepatic type), Neuromuscular (The perinatal, congenital, and childhood types) and Multisystem (Adult polyglucosan body disease).

7. Glycogen storage disease type V, also known as McArdle's disease

7.1. Background

Glycogen Storage Disease V or McArdle's disease, is an autosomal recessive metabolic cause of myopathy. Individuals with this disorder exhibit a deficiency or markedly reduced production of the glycogen phosphorylase enzyme (myophosphorylase) due to primarily nonsense mutations in the PYGM gene located on chromosome 11q13. Glycogen Storage Disease Type V, or McArdle's disease, is a metabolic myopathy characterized by exercise intolerance, manifesting as muscle pain (myalgia), rapid fatigue, and cramps during physical activity [48]. The primary identification of this disorder's cause was in 1959 as an inability to convertmuscle glycogen into lactate due to lack of myophosphorylase. It is an autosomal recessive disease caused by lack of one of the glycogen [49] metabolism enzymes. About 150 different causative variants in the responsible gene (*PYGM*) on chromosome 11q13 have beendetected [50]. The genetic variations are mostly missense mutations (about 50%), deletions (about 18%), nonsense mutations (about 13%), splice mutations (about 11%) and insertion/deletion or duplication variants which account for the remainder [51]. Most of these variants are located in exons and cause a significant decrease or complete loss of myophosphorylase enzyme function, mostly due to nonsense-mediated degradation (Table 7) [52,53].

7.2. Pathophysiology

This disorder is typically classified as muscle tissue disease (myopathy). The myophosphorylase enzyme is crucial for energy production, and its absence or deficiency in individuals with mutation primarily affects the ability of the muscle to perform exercises. As a result, the majority of patients exhibit exercise intolerance. This is the most common manifestation of glycogen storage in muscle, with very specific features observed through clinical examinations and investigations. [54]. There are two types of exercise: aerobic and anaerobic. Aerobic exercise, such as jogging, walking, light swimming, and cycling, relies on energy utilization by the muscles, which depends on various factors, including the intensity, type, and duration of the exercise, as well as diet and physical condition. Since aerobic activity favors the use of blood-derived substrates, such as fatty acids, it is better tolerated by patients with Glycogen Storage Disease V and thus valuable as a treatment modality. Anaerobic exercise, such as weightlifting, does not require oxygen to produce ATP and utilizes myophosphorylase for glucose production through the glycolytic pathway. This type of exercise is intense and cannot be sustained for ATP production in these patients. The anaerobic phase occurs during the initial minutes of exercise [55].

7.3. Biochemical features

Myophosphorylase protein can be detected using SDS-polyacrylamide gel electrophoresis and immune diffusion [56]. Very low levels of pyridoxine could be found in muscle of such patients. No major deletion or rearrangement of the phosphorylase gene has been detected using Southern blot DNA analysis. The enzyme may be absent or present at low levels [57].

8. Glycogen storage disease type 9

8.1. Background

GSD-9 is an uncommon hereditary condition that results in the body's inability to decompose glycogen, a complex sugar used for energy. The root cause of this disorder is an insufficient level of the enzyme phosphorylase kinase (PhK), which is critical for the process of glycogen breakdown. GSD-9 is a heterogeneous condition, meaning it has multiple subtypes, each with its own unique genetic cause and clinical presentation [58]. Glycogen storage disorder subtype 9 (GSD-9) is a hereditary disease characterized by a lack of hepatocellular kinase activity. Phosphorylase kinase is a complex enzyme consisting of four subunits, referred to as α, β, γ, and δ. The liver forms of subunits α, β, and γ are encoded by PHKA2, PHKB, and PHKG2, respectively. Abnormalities in these regions have been linked to GSD-9. The diversity of clinical symptoms, organ involvement, and disease severity (X-linked or autosomal recessive) complicates the diagnosis of GSD-9. In a study of patients from 12 families with suspected GSD-9, enzymatic testing was not diagnostic in five cases, making a reliable diagnosis difficult. Clinical symptoms included hypoglycemia, hepatosplenomegaly, short stature, hepatopathy, weakness, fatigue, and motor delay. Biochemical abnormalities included elevated glucose, uric acid crystals, and cholesterol levels (Table 8) [59].

8.2. Pathophysiology

Glycogen storage disease type IX (GSD IX) is caused by a deficiency of phosphorylase kinase. The enzyme is made up of four subunits, each with specific functions, and its structure and regulation are complex. The γ-subunit is responsible for the enzymatic activity of phosphorylase kinase, while the α- and β-subunits play a role in mitogen regulation, and the δ-subunit, called calmodulin, regulates the enzyme's Ca^{2+} requirement. The inhibitory effect of the a-subunit, a 138-kDa enzyme within the phosphorylase kinase complexes, can be abolished by protein kinase (PKA). Phosphorylation occurs at seven cysteine residues within a "multiphosphorylation region" at the N terminus of the subunit, according to research employing the rabbit muscle version of the subunit. Autophosphorylation by phosphorylase kinase can also occur in this domain [59]. The a-subunit isoforms found in muscle and liver are encoded by the genes PHKA1 and PHKA2, respectively, which are located on the X chromosome in regions Xq12-q13 and Xp22.2-p22.1. These genes consist of 32 and 33 exons, respectively, and undergo tissue-specific homologous recombination, leading to some transcripts skipping exons 28 and/or 29. X-linked glycogenosis (XLG) is caused by PHKA2 mutations and is characterized by hypoglycemia, distention, chronic liver disease, learning disability, decreased motor function,high cholesterol, triglyceride levels, and hyperketosis after feeding. Typically, these symptoms improve during adolescence. XLG, an X-linked genetic disorder caused by mutations in PHKA2, has been classified into two subtypes: XLG1 and XLG2. XLG1 is distinguished by the lack of phosphorylase kinase activity in both the liver and erythrocytes, whereas XLG2 has regular activity in erythrocytes but is inadequacy in the liver. XLG1 has a wide array of mutations, whereas mutations responsible for XLG2 are mostly missense or minor in-frame deletions or intronic variations that primarily affect proteins clustered around the subunit's amino terminus. X-linked phosphorylase kinase deficiency in muscle is caused by mutations in the PHKA1 gene, leading to various symptoms including exercise intolerance, cramps, myalgia, weakness, and myoglobinuria [58].

8.3. Conclusion

Glycogen storage disorder type 9 (GSD-9) is a disease caused by a mutation that results in a deficiency of the enzyme phosphorylase kinase (PhK), leading to an inability to break down glycogen. There are multiple subtypes of GSD-9, each with its unique genetic cause and clinical presentation. The symptoms of GSD-9 can vary from patient to patient, but they generally include fatigue, muscle weakness, and exercise intolerance. Treatment is primarily supportive, with a focus on managing symptoms and preventing complications, and in some cases, liver transplantation may be necessary to address liver dysfunction or failure. With proper management, individuals with GSD-9 can lead full and productive lives. Diagnosis of GSD-9 involves clinical evaluation, biochemical testing, and genetic analysis. Phosphorylase kinase deficiency and the variations in its α, β, and γ subunits, which are produced from distinct genes or by transcriptional variants of a single gene, result in complex clinical symptoms and inheritance patterns.

9. Glycogen storage disease type X

9.1. Introduction

Glycogen storage diseases (GSDs) are indeed a set of hereditary disorders defined by glycogen accumulation in diverse organs and tissues due to enzyme deficiencies in glycogen metabolism [61]. There are currently 14 recognized types of GSDs, with varying clinical presentations and genetic mutations. GSD type X is a rare subtype of

Table 8. Brief description of GSD 9.

Type of GSD/ Another name	*Defective enzyme or other/ Inheritance type*	*Defective gene and location in chromosome*	*Incidence in the world*
GSD IXa	Phosphorylase kinase (α2 subunit)	PHKA2 (X-linked)/ Xp22	Varying
GSD IXb	Phosphorylase kinase (β subunit)	PHKB/16q12	
GSD IXc	Phosphorylase kinase (γ subunit)	PHKG2/16p11	
GSD IXd	Phosphorylase kinase (α1 subunit)	PHKA1/ Xq13	

Table 9. Brief description of GSD X.

Type of GSD/Another name	*Defective enzyme or other/ Inheritance type*	*Defective gene and location in chromosome*	*Incidence in the world*
Glycogen storage disease type X (GSD type X)	Muscle phosphoglycerate mutase	PGAM2 in 7p13	Varying

GSDs that was first described in 2007. It is caused by a lack of the enzyme muscle phosphoglycerate mutase [62]. The exact prevalence of GSD type X is unknown, but it is believed to be a rare disorder (Table 9).

9.2. Pathophysiology

Due to the rarity of GSD type X, there is limited knowledge of its pathophysiology and natural history. More research is needed to elucidate the molecular mechanisms underlying the disorder and to develop targeted treatments that can improve outcomes for affected individuals.

9.3. Conclusion

In conclusion, Glycogen storage disease type X (GSD X) is a rare genetic disorder that affects the metabolism of glycogen in the liver, leading to liver enlargement and elevated liver enzymes. It is passed down in an autosomal recessive way, and the gene that causes the condition is unknown. Clinical characteristics, laboratory testing, and imaging investigations are used to make the diagnosis. Treatment is focused on managing symptoms and preventing complications, such as avoiding fasting and maintaining a high-carbohydrate diet. In severe cases, liver transplantation may be necessary. The prognosis for individuals with GSD X is generally good, although rare cases can progress to severe liver disease. Further study is required in order to better comprehend the disease's natural history and find viable treatments.In the meantime, early diagnosis and proper management can improve outcomes for individuals with GSD X. This rare condition should be known to healthcare providers and they should consider it in the differential diagnosis of liver enlargement, particularly in individuals with a family history of the disease. GSD type X is a novel addition to the glycogen storage disorder family and is regarded as one of the rarest varieties. It was discovered in a small group of individuals with mysterious hypoglycemia and has subsequently been described in a few hundred cases around the world. The clinical presentation of GSD type X can vary widely, and some individuals may not develop symptoms until later in life.

10. Glycogen storage disease type XI

10.1. Background

Glycogen storage disease type XI or Fanconi Bickel Syndrome, is a rare kidney tubule function disorder that results in increased excretion of certain amino acids, bicarbonate, phosphates (phosphorus salts), glucose, and uric acid in the urine. A few of the various names for this ailment include Fanconi Bickel Syndrome, Lactate Dehydrogenase, Hepatorenal glycogenosis with renal Fanconi syndrome, Hepatic glycogenosis with amino aciduria and glucosuria, Fanconi syndrome with intestinal malabsorption and galactose intolerance, Pseudo-Phlorizin diabetes, Glycogenosis Fanconi type, etc. It was previously classified as GSD type 11, but now GSD type 11 is considered a deficiency in LDHA enzyme [62-64].

10.2. Pathophysiology

Numerous mechanisms can result in diminished reabsorption of solutes by the proximal tubule.

The 3 main categories in which they can be classified are: alterations in the function of the carriers that transport substances across the luminal membrane; disturbances in cellular energy metabolism; and changes in permeability characteristics of the tubular membranes. The proximal tubules use specialized transporters and channels to reabsorb proteins and solutes. These are found in the luminal or basolateral membranes of tubular cell structures. The management of acid-base balance, mineral homeostasis, and drug removal are other functions of the tubules. In Fanconi syndrome, the solutes are unable to pass through the proximal renal tubule cell's apical network. Substantial proteins, electrolytes, and other solutes are lost as a result of the patients'significant biochemical and transport carrier abnormalities. These carriers carry amino acids, glucose, phosphate, and bicarbonate [62].

Currently, there isn't a clear model or mechanism that emphasizes knowledge of pathophysiology. Recent data, however, backs up the widely accepted view that the proliferation of flawed transporters is what causes the waste of solutes. It is highly likely that the combination of metabolic diseases reduces the availability of adenosine triphosphate (ATP) necessary for the activity of the Na+/K+ ATPase enzyme. Consequently, this leads to a significant decrease in the electrochemical gradient required for effective solute transport across cell membranes [63,64]. The most prevalent genetic cause of Fanconi syndrome is cystinosis, which develops when cystinosin's activity is compromised as a result of a mutation in the CTNS gene, which results in the accumulation of intralysosomal cystine [65]. The infantile type of cystinosis, which is characterized by significant renal proximal tubular dysfunction during the first year of development, then develops early as a result of this. Cystinosin is a proton-driven transporter that exports cystine from lysosomes and performs this function [66]. The relationship between intralysosomal cystine buildup and Fanconi syndrome is not supported by enough evidence [64,65].

11. Brief mention of current standard treatments or emerging therapies for specific types of GSDs

Only a brief mention is given since the current standard treatments or emerging therapies are too broad and beyond the scope of our research. Maintaining glucose homeostasis with dietary control and the use of uncooked cornstarch is the current therapy objective. Other therapeutic options for both disease symptoms and long-term consequences include enzyme replacement therapy (ERT), physical and supportive therapies, pharmaceutical treatment, and organ transplantation, in addition to nutritional measures. Since there isn't a specific treatment for GSDs, attempts are being made to create novel approaches, such as gene

therapy. The usual therapies for glycogen storage disorders (GSDs) vary depending on the type. Frequent meals high in complex carbohydrates, cornstarch therapy, and ongoing glucose monitoring are all part of the standard treatment for GSD Type I (Von Gierke Disease). Gene therapy and liver-targeted enzyme replacement treatments are examples of emerging treatments. The usual treatment for GSD Type II (Pompe Disease) is glucosidase alfa administered as part of enzyme replacement therapy (ERT). A new strategy that is showing promise in clinical trials is gene therapy. GSD Type III (Cori/Forbes Disease): Supplementing with cornstarch and eating a high-protein diet are the treatment options. Gene therapy and enzyme replacement are still being researched. Liver transplantation is currently the primary treatment for severe instances of GSD Type IV (Andersen Disease). The goal of experimental treatments is to alter the synthesis of glycogen. Although there is no known cure for GSD Type V (McArdle Disease), symptoms can be managed with dietary changes, aerobic activity, and creatine supplements. The use of gene therapy is being investigated [67,68].

12. Patient perspectives of GSDs

The majority of GSD patients lead independent adult lives and manage their circumstances effectively, despite the fact that GSDs are a severe group of disorders that necessitate lifelong therapy with rigorous adherence. Doctors who work with patients who have GSD should help them become independent as soon as possible and talk to them about essential issues like family planning, eating habits, and medical monitoring. In addition to improving patient knowledge, patient organizations that facilitate communication between peers of the same age may also offer emotional and mental support. GSDs affect the mental and physical capacities of both parents and offspring. Children with both skeletal myopathy and cardiomyopathy had lower quality-of-life scores [69].

13. Animal models for the investigations into future treatment modalities

GSD I (glucose-6-phosphatase deficiency) in mice, GSD II (acid α-glucosidase deficiency) in dogs, cattle, and quail, GSD III (debrancher enzyme deficiency) in dogs, and GSD VIII (phosphorylase kinase deficiency) in rats and mice have all been found to have spontaneous animal counterparts. Rats (Acarbose-induced GSD II-like conditions, iodoacetate-induced symptoms of myophosphorylase (GSD V) and myophosphofructokinase (GSD VII) deficiency) and chickens (ochratoxin A-induced symptoms of cyclic AMP-dependent protein kinase deficiency) have both been shown to exhibit experimentally induced GSD-like conditions. In the generated animal settings, enzymatic abnormalities that are characteristic of the human GSD types have not been convincingly found. It is discussed how the kinds of GSD in humans and animals are similar [70].

14. Future directions for research in glycogen storage diseases

There is a vast need for a multidisciplinary approach in treatment to optimize patient outcomes. Furthermore, the emphasis on genetic testing reflects advancements in medical diagnostics that can lead to more precise treatment plans. For the most part, molecular genetic testing is accessible and benign for the diagnosis of many uncommon genetic conditions. Invasive liver and muscle biopsies are no longer necessary in certain situations due to genetic testing. There is presently no cure for GSDs, and the majority of treatments focus on reducing symptoms. Preventing and controlling hypoglycemia, hyperlactatemia, hyperuricemia, and hyperlipidemia are important objectives. Consuming starch can help prevent hypoglycemia; a commercially accessible, physically altered version is currently in use. An antiketogenic diet significantly reduces the size and glycogen content of the liver in people with GLUT2 deficiency. Statins are used to treat hyperlipidemia, while allopurinol is used to treat hyperuricemia. Recombinant alglucosidase alfa, which aids in the breakdown of lysosomal glycogen, is now used in enzyme replacement therapy (ERT) to treat certain GSDs, including GSD type II. The possible application of ERT for different types of GSD is also being investigated. Patients who have developed hepatic malignancy or failure due to specific GSDs should be evaluated for liver transplantation. Although hepatic failure and hypoglycemia can be treated with this operation, the cardiomyopathy linked to GSD is not addressed, and it may worsen. The safety and bioactivity of adeno-associated virus vectors are being assessed in Phase I and Phase III clinical studies for gene therapy for Pompe disease and GSD Ia, respectively. Understanding the natural history and evolution of GSDs through clinical research yields important outcome metrics that are used as endpoints in clinical studies to assess benefits. Despite their promise, gene therapy and genome editing have obstacles to overcome before they can be used in clinical settings. These obstacles include immune responses and toxicities that have been identified during ongoing gene therapy clinical trials. An unmet need for targeted, long-lasting treatment for glycogen storage disorders is being addressed by the development of gene therapy [71-73]. The pathophysiology and biology of GSD-Ia and GSD-Ib have been outlined by animal models, which have also aided in the development of successful gene therapy approaches for these conditions. Preclinical research on GSD-I has demonstrated the safety and effectiveness of gene therapy for GSD-Ia and GSD-Ib mediated by recombinant adeno-associated virus vectors. As of 2023, rAAV-mediated gene augmentation treatment for GSD-Ia (NCT05139316) is undergoing a phase III clinical trial. In 2022, mRNA augmentation for GSD-Ia was the subject of a phase I clinical investigation (NCT05095727). Gene editing and other alternative genetic technologies for GSD-I treatments are also being investigated for their potential to enhance further long-term results [68,72].

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