

DISORDERS OF CARBOHYDRATE METABOLISM

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6.1 INTRODUCTION

Many clinical conditions arise because of deficiency of one or more enzymes catalyzing the metabolic pathways of macronutrients. The deficiency could be either due to genetic defect or mutations. Consequently, these molecules are not metabolized efficiently resulting in accumulation of deficiency of certain metabolites. These abnormal levels manifest as diseases at physiological levels. In this unit, we shall discuss about disorders of carbohydrate metabolism. Since, glucose is the central molecule of carbohydrate metabolism, therefore, a brief overview of carbohydrate metabolic pathways will be presented. This is followed by the discussion as to how these pathways are coordinately regulated to maintain certain levels of blood glucose. Principle cause and symptoms of common metabolic disorders of carbohydrates will be explained. Clinical tests recommended for their detection will also be outlined.

Expected Learning Outcomes

After studying this unit, you should be able to:

- ❖ explain how pathways of synthesis and degradation of carbohydrates are coordinately regulated;
- ❖ discuss how glucose homeostasis is maintained;
- ❖ elaborate the cause, symptoms and diagnostic tests for galactosemia, glycogen storage diseases, pentosuria and diabetes mellitus; and
- ❖ describe the methods used for measurement of glucose in clinical specimen such as blood and urine.

6.2 BRIEF OF CARBOHYDRATE METABOLIC PATHWAYS

Carbohydrates are the major source of energy in living cells. The monosaccharide glucose is the central molecule in carbohydrate metabolism since all the major pathways of carbohydrate metabolism are connected with it. The other monosaccharides like fructose, galactose and mannose also enter the same routes after transformation into glucose or intermediates of glucose metabolism.

Carbohydrate metabolism in a typical animal cell is predominately glucose metabolism. Glucose metabolism includes several important pathways which you have learnt in the course "Concepts and connections in metabolism- MBC005". These include; (1) glycolysis, (2) citric acid cycle (TCA cycle), (3) hexose monophosphate shunt (HMP shunt), (4) gluconeogenesis, (5) glycogen metabolism (glycogenolysis and glycogenesis), (6) uronic acid pathway (7) Cori cycle and (8) glucose- alanine cycle. All these metabolic pathways of glucose metabolism are interconnected (Fig. 6.1).

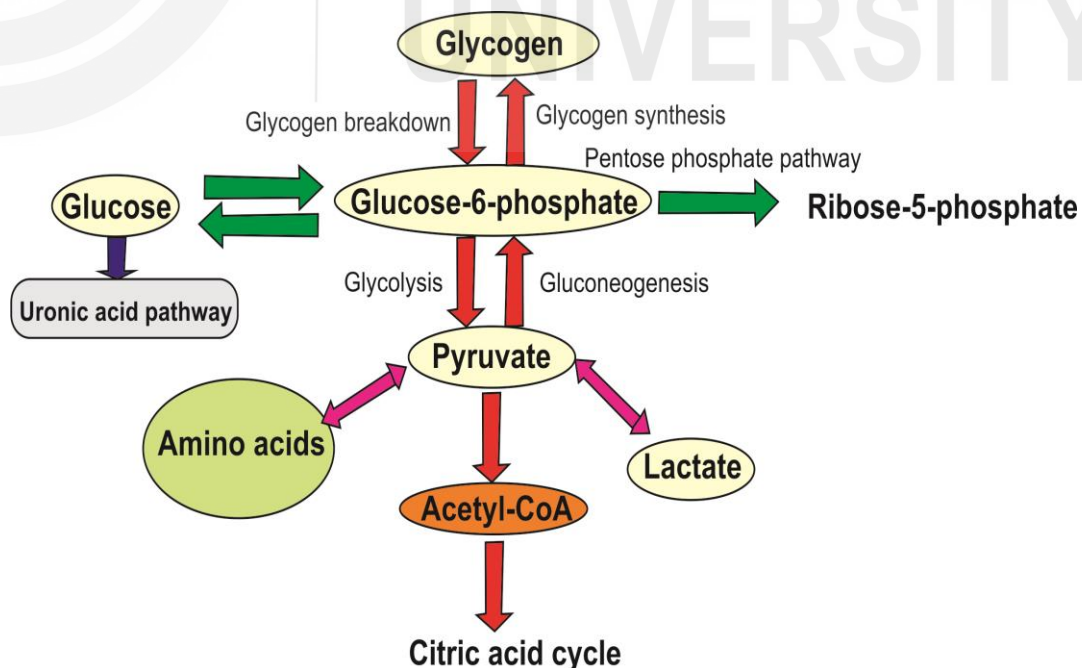


Fig. 6.1: An overview of interconnected pathways of carbohydrate metabolism.

Lets us briefly revise the pathways involved in glucose metabolism and their interconnectivity.

Glycolysis and its connectivity to other pathways

The oxidation of glucose to pyruvate is called glycolysis. It is a universal pathway of incomplete oxidation of glucose under both aerobic and anaerobic conditions. In addition to glycolysis, pyruvate is also formed from the catabolism of glucogenic amino acids, decarboxylation of malate by malic enzyme, transfer of amino group of alanine and oxidation of lactate.

The fate of pyruvate varies depending on the presence or absence of oxygen and the needs of the organism. Under aerobic conditions, it is completely oxidised by TCA cycle while in times of vigorous muscular activity when oxygen is limiting, pyruvate is fermented to lactate. The latter is then converted to glucose by gluconeogenesis in the liver and released into circulation for use by muscles (Cori cycle). Finally, pyruvate can provide the carbon skeleton for amino acids.

TCA cycle and its connectivity to other pathways

TCA cycle is the convergent pathway for complete oxidation of carbon derived from carbohydrates, fats and amino acids. It is an amphibolic pathway as it is involved in both catabolism and anabolism. Reducing equivalents (NADH and FADH₂) formed during TCA cycle are re-oxidized by mitochondrial electron transport chain and coupled to ATP synthesis (oxidative phosphorylation) that accounts for most of the ATP produced under aerobic conditions. The intermediates of TCA cycle are also anabolic precursors for the synthesis of amino acids, heme and fatty acids. Krebs cycle is the most important central pathway connecting almost all individual metabolic pathways (either directly or indirectly).

Gluconeogenesis and its connectivity to other pathways

Gluconeogenesis is the production of glucose from non-carbohydrate precursors. It shares seven out of the ten reactions of glycolysis (link with glycolytic pathway) but includes three unique, irreversible steps that permit **reciprocal regulation** of both pathways. These are at steps between pyruvate and phosphoenol pyruvate; fructose-1,6-bis-phosphate and fructose-6-phosphate and glucose-6-phosphate and glucose. The production and release of glucose is restricted to liver and to a limited extent few other organs. In organs that do not express glucose 6-phosphatase, glucose 6-phosphate cannot leave the cell and is fed to multiple pathways depending on the needs and enzyme profile.

Hexose monophosphate pathway and interconnected pathways

Hexose monophosphate or oxidative pentose phosphate pathway is active in tissues engaged in reductive biosynthesis or require NADPH for maintaining specific constituents in a reduced state. Some of these tissues / organs include liver, adipose tissue, adrenal cortex, lactating mammary gland, lens, cornea of eye and red blood cells. The pathway occurs in the cytosol and can be divided into two phases: **oxidative phase** (generates NADPH) and **non-**

oxidative phase (synthesizes pentose-phosphate and other phosphate monosaccharides). It begins with glucose 6-phosphate, an intermediate that can enter multiple routes including glycolysis. The non oxidative branch interconverts sugars and provides a connecting link with glycolysis. The sugars such as erythrose 4-phosphate and ribose 5-phosphate are precursors for aromatic amino acid and nucleic acids synthesis, respectively.

Glycogen metabolism and its connectivity to other pathways

Glycogenesis is the synthesis of glycogen from glucose. The liver and skeletal muscles are the major sites but it also occurs in every tissue to a limited extent. Initially, a linear polymer of glucose is made by transfer of glucose residues from an activated donor (UDP-glucose) by glycogen synthase to preformed glucose primer (glycogenin). Subsequently branching enzyme introduces branches.

Glycogenolysis is the breakdown of glycogen to glucose 1-phosphate by phosphorolysis catalysed by glycogen phosphorylase. The debranching enzyme removes the branch point residue to allow phosphorylase to continue acting. Glucose 1-phosphate is converted to glucose 6-phosphate which can enter glycolysis, pentose pathway or converted to glucose and released to maintain blood glucose levels.

Cori cycle and its connectivity to other pathways

The Cori cycle involves the conversion of muscle glycogen to lactate during intense muscular activity and low oxygen. The muscle gains time by regenerating NAD^+ and continuing glycolysis. It shifts lactate to the liver for gluconeogenesis. The released glucose is taken up by the muscle for its use or conversion back to glycogen. Thus, Cori cycle links gluconeogenesis with anaerobic glycolysis.

6.2.1 Hormonal Regulation of Carbohydrate Metabolism

The essence of carbohydrate metabolism lies at maintenance of blood glucose levels. Rise in blood glucose levels such as following meals is brought down by promoting (i) its uptake by cells and utilization for energy through glycolysis, TCA and oxidative phosphorylation pathways (ii) storage as glycogen in liver and muscle as short-term energy reserve and (iii) conversion to triacylglycerols in adipose tissue. At the same time, pathways which generate glucose such as gluconeogenesis and glycogenolysis are inhibited.

Liver primarily has processing and distribution function by providing all other organs and tissues with an optimum level of nutrients via the bloodstream. The role of liver is so important that the whole organ system is divided into hepatic and extra hepatic. Liver and kidney are responsible for the synthesis of the glucose, whereas brain, muscle, blood cells and other extra hepatic tissues utilize glucose for energy.

The inter organ coordination of carbohydrate metabolism is mediated by hormones which fall broadly into two groups based upon their role:

(a) Those which exert a fundamental regulatory influence; their normal function being essential for optimal carbohydrate metabolism, for example, hormones of pancreatic islet cells especially insulin and glucagon and hormones of adrenal cortex and anterior pituitary.

(b) Those which influence carbohydrate metabolism, but are not essential for its auto regulation under normal physiological conditions, e.g. thyroid hormones.

When blood glucose concentration is high, insulin secreted by pancreatic β cells promotes glucose uptake by cells and its oxidation through glycolysis to lower glucose levels. It also inhibits enzymes of glycogenolysis and promotes glycogenesis. On the other hand, when glucose concentration drops, such as several hours after a meal or during exercise, glucagon released by pancreatic α - cells promotes gluconeogenesis and glycogenolysis and release of glucose by the liver to raise the blood glucose levels. Glucagon promotes uptake of amino acids from the blood by liver hepatocytes, and convert them to glucose. A rise in blood glucose levels inhibits glucagon via a negative feedback mechanism. Thus, insulin and glucagon help to maintain glucose homeostasis.

In addition to these two hormones, cortisol secreted by adrenal cortex affects by increasing blood glucose level by gluconeogenesis from amino acid pool and diminishing peripheral uptake and utilization of glucose. It also increases liver glycogen with the increased activity of glycogen synthase.

Growth hormone and ACTH (adrenocorticotropin) secreted by the anterior pituitary hormones raise the blood glucose level and antagonize the effect of insulin as their secretion is stimulated by hypoglycemia. Thyroxine, a thyroid hormone accelerates hepatic glycogenolysis, with consequent rise in blood glucose. Thyroid hormones may also increase the rate of absorption of hexoses from the intestine and also increased hepatic glucose-6-phosphatase activity. Rate of protein catabolism is increased by excessive thyroid hormones and thus increases gluconeogenesis from amino acids.

Let us put this information in terms of glucose homeostasis.

6.3 GLUCOSE HOMEOSTASIS

Carbohydrate homeostasis refers to the regulation of blood glucose levels in animals. The normal blood glucose level is 60 to 100 mg per deciliter (mg/dl) in fasting state and 100 to 140 mg/dl following food ingestion. The blood glucose level is maintained by a balance of factors that dictate the rate of glucose entry vs. removal from blood (Fig. 6.2) and liver plays a major role in this. Let us understand about these in detail.

(i) Release of glucose into blood

Blood glucose is derived exogenously from dietary sources and endogenously predominantly from the liver. When blood glucose levels are low, various pathways come into action in response to hormonal signals; synthesis of glucose by gluconeogenesis and glycogenolysis is stimulated to produce

glucose. At the same time, utilization of glucose by glycolysis is inhibited and liver consumes fatty acids as fuel to release glucose into blood.

(ii) Removal of glucose from blood

The blood glucose is removed by many tissues / organs. Brain, muscles, liver and RBC are some of the major targets of glucose uptake. They oxidize it to supply energy for various activities; glycogenesis in muscles and liver; transmission of electrical impulses in brain, formation of lactose (sugar of milk) in lactating mammary gland, synthesis of glycoproteins/ glycolipids and production of ribose sugars for nucleic acid synthesis. The adipose tissue is the major site of converting excess glucose into storage fat (triacyl glycerol).

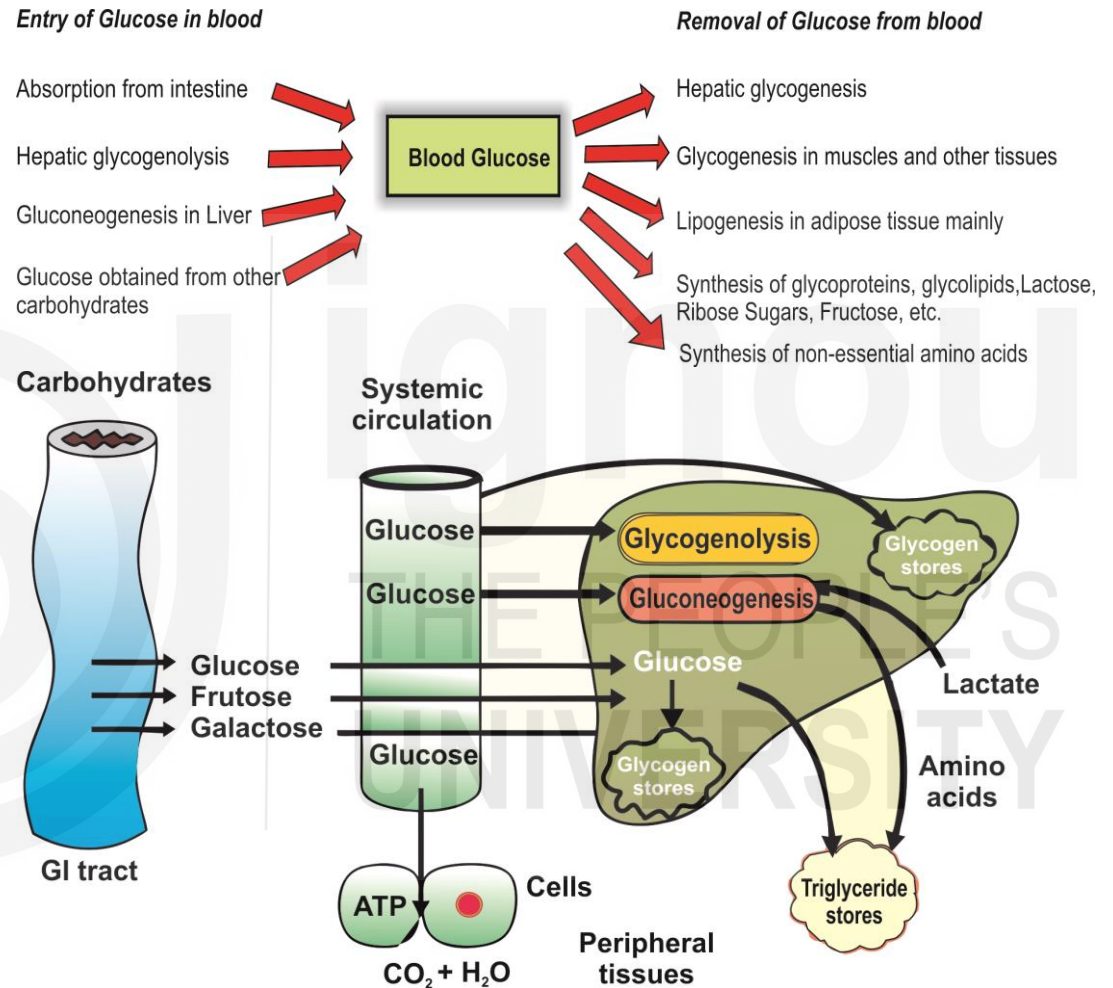


Fig 6.2: Blood glucose homeostasis.

SAQ 1

- a) The normal blood glucose level in fasting state is and following meals.
- b) Enzymes of glycogenolysis are inhibited by hormone and promoted by hormone.

6.4 DISORDERS OF CARBOHYDRATE METABOLISM

Conditions that disturb glucose homeostasis result in altered blood glucose levels; either hyperglycaemia (increase) or hypoglycaemia (decrease). These conditions may arise due to inborn errors of metabolism or develop later in life due to environmental factors, unhealthy life style or work related factors.

Diseases due to inborn errors of carbohydrate metabolism occur due to defects at genetic level, consequently either the enzyme is not formed in sufficient amounts or it is not functional. These include galactosemia, glycogen storage diseases, pyruvate carboxylase deficiency, fructose-1,6-bisphosphatase deficiency, hereditary fructose intolerance, pentosuria and glucose-6-phosphate dehydrogenase deficiency. A common disease associated with carbohydrate metabolism is diabetes. It may arise due to the genetic disposition or may be acquired due to life style. Common feature of these disorders is either absence of a metabolite or its excessive accumulation that affects other interconnected metabolic pathways.

6.4.1 Galactosemia

Galactosemia is a condition in which body is unable to metabolize galactose. Galactose is primarily part of milk sugar, lactose that is present in milk and milk products. Many fruits like avocado, apples, banana and sweet potato also contain galactose in small amounts.

This autosomal recessive hereditary disorder is caused by the deficiency of any of the enzyme in Leloir pathway. You may recall the Leloir pathway of galactose metabolism shown in Fig. 6.3. Classical galactosemia is most common form that is caused due to deficiency of galactose-1-phosphate uridylyl transferase (GALT) enzyme. As a result, such patients accumulate excess of galactose 1-phosphate and galactitol. Patients with classic galactosemia are asymptomatic at birth, but develop life threatening complications after exposure to milk. Symptoms include feeding difficulties, hypoglycemia, renal tubular dysfunction, vomiting, diarrhoea, hepatomegaly, *Escherichia coli* sepsis, and cataract. Long-term complications can include speech and cognitive disabilities, decreased bone mass and hypergonadotrophic hypogonadism in the majority of females.

Galactosemia due to deficiency of Galactokinase (GALK) caused by mutation in its gene is very rare and results in an accumulation of galactose in the blood and tissues. Such patients may be able to tolerate milk products but can develop cataracts due to high galactose and galactitol levels in their blood. Third type of galactosemia is caused by deficiency of the enzyme UDP-galactose-4'-epimerase (GALE). These patients also accumulate galactose and galactose-1-phosphate in erythrocytes as well as high levels of UDP-galactose. However, such patients rarely show the symptoms as the enzyme deficiency is usually restricted to red and white blood cells.

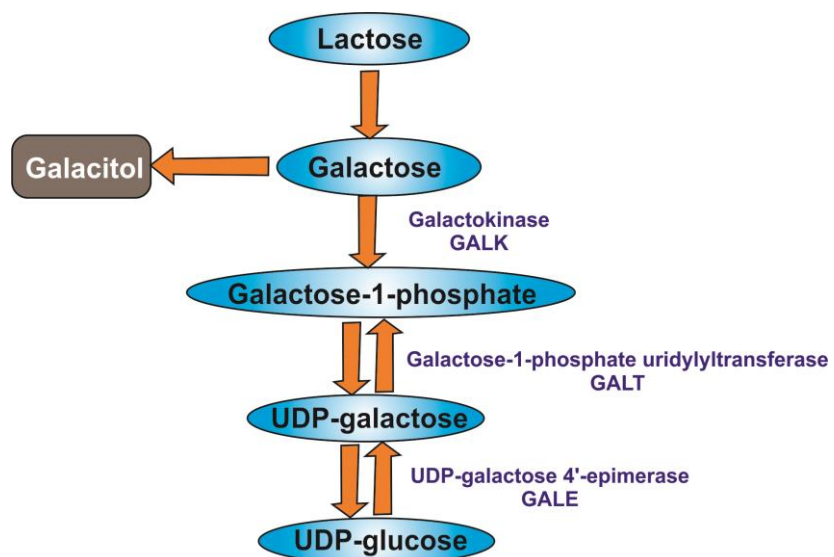


Fig. 6.3: Leloir pathway of galactose metabolism.

Treatment involves immediate dietary restriction of galactose containing foods. For infants, milk is replaced by soy milk or formula containing other carbohydrate sources, or amino acid-based formulas. Presence of reducing sugar in urine with confirmation of absence of glucose may indicate the disease; however, it is to be confirmed with more specific tests measuring enzyme activity of GALT and GALK. In diagnostic laboratories, gas-chromatographic determination of urinary sugars and sugar alcohols demonstrates elevated concentration of galactose and galactitol and is used for detection of galactosemia.

Another test is Beutler test that is also known as heel prick test. It is a screening test done for new borne babies and is fluorescence based semi-quantitative rapid test that detects the generation of nicotinamide adenine dinucleotide phosphate (NADPH) from nicotinamide adenine dinucleotide phosphate (NADP). The test is positive if the blood spot fails to fluoresce under ultraviolet light. However, the test is not reliable in detecting female heterozygotes and if required molecular testing is done to confirm the diagnosis.

6.4.2 Glycogen Storage Diseases

Glycogen storage diseases (GSD) are the group of inherited diseases that affect glycogen metabolism. Mutations are found in the genes encoding the enzymes that regulate its processing, leading to abnormal concentrations or structures. Glycogenolysis, gluconeogenesis, and the production of lactate and ketone bodies can be affected, depending on the disorder. A short synopsis of GSD is presented in Table 6.1. The diseases have been numbered from Type 0 to Type 12.

A close look at the Table 6.1 gives you the idea that these diseases primarily affect liver and muscles, the major organs involve in glycogen storage. Depending on the deficiency there may be massive increase in the amount of glycogen and / or abnormal structure. The diseases numbered Type I to VII mentioned here have an autosomal recessive pattern of inheritance.

Table 6.1: Glycogen storage diseases in humans.

Type/ Name	Defective enzyme / amount & structure of glycogen	Organs (s) involved	Clinical Symptoms
Type 0	Glycogen synthase Decreased liver glycogen content, structure is normal	Liver	Hypoglycemia and ketosis after short-term fasting and hyperlipidemia as excess glucose cannot be converted to glycogen
Type 1 von Gierke disease	Glucose-6-phosphatase (in 80%)	Liver and kidney	Enlarged liver, kidney failure, hypoglycemia leading to seizures, lactic acidosis, hyperlipidemia, hyperuricemia & Gout; cholesterol deposits, renal tubular acidosis, platelet dysfunction
Type 1b von Gierke disease	Glucose 6-phosphate translocase (in 20%) Increased glycogen; normal structure in both.		Type1b patients also show low number of white blood cells, dysfunctional neutrophils, increased susceptibility to infections and poor wound healing.
Type II (Pompe disease) also classified as lysosomal storage disease	Lysosomal acid- α -glucosidase Increased glycogen in skeletal, cardiac and smooth muscles; normal structure	All organs	Enlarged liver and heart. Weakness, hypotonia, respiratory distress, poor linear growth and weight gain. Nervous system is also affected. Death occurs at an early age.
Type III (Cori or Forbes disease)	Glycogen debranching enzyme Increased amount of glycogen with abnormal structure	Liver, skeletal and cardiac muscle	Enlarged liver and spleen in infants, cirrhosis, Accumulation of abnormal glycogen; hypoglycemia with ketosis, myopathy and symptoms are like type- I but milder.
Type IV (Anderson disease)	Branching enzyme Normal amount; long outer branches	Liver, skeletal muscle, spleen	Enlarged liver and spleen; myoglobin in urine; muscular atrophy, myopathy, central and peripheral nervous system dysfunction, liver failure leads to early death
Type V (Mc Ardle disease)	Muscle glycogen phosphorylase Normal structure but moderate increase in glycogen;	Skeletal muscle	Exercise induced cramps and pain, myoglobin in urine. Generally, lactate does not accumulate

Type VI (Hers disease)	Liver Glycogen phosphorylase Increased glycogen	Liver	Enlarged liver, mild liver dysfunction, Liver glycogen cannot be converted to glucose. Symptoms are milder to type I disease.
Type VII (Tarui disease)	Muscle Phosphofructokinase-I Normal but increased amount of glycogen	Skeletal muscle, RBC	Symptoms like type V. Hemolytic anemia and hyperuricemia may also occur.
Type IX	Phosphorylase kinase	Liver	Mild symptoms, liver enlargement and ketosis following short fasting

Since the disease affects multiple organs and function, therefore, laboratory testing for GSDs should include glucose, electrolytes, liver function tests, complete blood count, creatine kinase, uric acid, cholesterol, triglycerides, ammonia, and lactate, preferably after the patient has fasted. Liver biopsy shows hepatocytes bulging with glycogen and a vacuolated appearance. Enzyme assays are poor choice as the diagnostic tools because of difficulty in performing. Genetic testing has replaced these tests due to its ready availability and non-invasiveness.

Treatment for most GSDs is dietary management with goal to maintain normal blood glucose levels.

6.4.3 Pentosuria

Essential pentosuria refers to the condition characterized by high levels of a pentose sugar, L-xylulose in urine. Despite the excess sugar, affected individuals have no associated health problems. It is a rare disease and occurs almost exclusively in individuals with Ashkenazi Jewish ancestry. Approximately 1 in 3,300 people in this population are affected. Affected enzyme is L-xylulose reductase that converts xylulose to xylitol, as a result excess sugar is released in urine.

While essential pentosuria is a genetic disease, alimentary pentosuria is non-inherited which may occur following intake of excessive amounts of fruits high in L-xylulose or another pentose called L-arabinose. However, the condition disappears when diet is changed.

The disorder is diagnosed through specialised urine tests by detecting the sugar, L-xylulose in the urine. People with the disorder show an excretion of 1 to 4 grams of L-xylulose in the urine per day. However, since the disease is not associated with any health condition, therefore, no treatment is needed.

6.4.4 Inborn Errors of Fructose Metabolism

Fructose is naturally present in high concentrations in fruits, honey; however, it is also present in increasing number of processed foods in the form of high fructose corn syrup (HFCS). Inherited disorders of fructose metabolism include

essential fructosuria that occurs due to deficiency of fructokinase resulting in elevated levels of fructose in urine and blood. However, this is an asymptomatic disorder and therefore not of clinical significance.

Another group of disorders is hereditary fructose intolerance (HFI). It is seen in individuals having mutations in gene encoding for the enzyme aldolase B. Aldolase B catalyses the specific and reversible cleavage of fructose-1,6-fructose-1-phosphate (F1P) into dihydroxyacetone phosphate and D-glyceraldehyde (Fig. 6.4). As a result, high levels of fructose-1-phosphate accumulate. The enzyme is normally expressed in liver, renal cortex and small intestine.

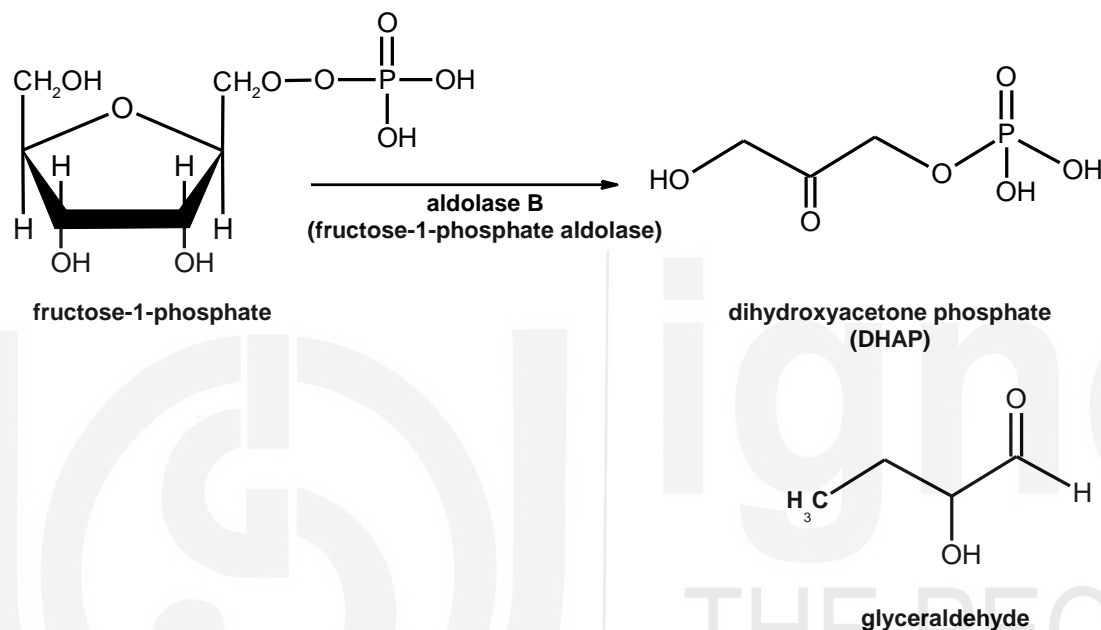


Fig. 6.4: Reaction catalysed by aldolase B.

The incidence of HFI is on the order of 1 in 20,000 live births. Neonates with HFI are generally healthy and only start showing up the symptoms only after they are weaned off the milk and exposed to diet containing fructose, sucrose or sorbitol in fruits and vegetables. The disorder is characterized by severe hypoglycemia and vomiting following fructose intake. Prolonged intake of fructose by infants with this defect leads to vomiting, poor feeding, jaundice, hepatomegaly, hemorrhage, and eventually hepatic failure and death. Patients will remain symptom free on a diet devoid of fructose and sucrose.

HFI patients will also develop metabolism dysfunction-associated fatty liver disease (MAFLD), also known as non-alcoholic fatty liver disease (NAFLD).

The primary cause of the manifesting symptoms in HFI is the trapping of inorganic phosphate (Pi) in fructose-1-phosphate and the consequent reduction in the pool of ATP via the fructokinase reaction. The trapping of the inorganic phosphate pool and ATP depletion leads to global reduction in all cellular processes that rely on phosphorylation or ATP. The loss of the inorganic phosphate pool impairs glycogen breakdown due to the role of Pi as a substrate for the phosphorolysis action of hepatic glycogen phosphorylase.

This, therefore, contributes to the severe hypoglycemia upon ingestion of fructose or sucrose.

HFI is also seen in case of hereditary deficiency of hepatic fructose-1,6-bisphosphatase (F1,6BPase) enzyme, that is a very rare autosomal recessive. Symptoms include severely impaired hepatic gluconeogenesis that leads to episodes of hypoglycemia, apnea, hyperventilation, ketosis and lactic acidosis, seizures, hepatomegaly, hyperlipidemia, hepatosteatosis, and liver damage. The severity of these symptoms increases when carbohydrate is insufficient in the diet. These symptoms can take on a lethal course in neonates particularly in the absence of carbohydrate intake.

Patients with HFI have elevated levels of fructose-1-phosphate, but there is not a clinical test available for this biomarker. Discovery of fructose in the urine can suggest a disorder of fructose metabolism, but the absence of fructosuria does not rule out these conditions due to variation in the timing of the fructose ingestion. After collecting an extensive dietary and nutritional history of the patient, the least invasive and most common method of diagnosis for both HFI and FBP is DNA analysis. If no mutations are found, then determination of enzymatic activity from liver biopsy can be performed.

The treatment for HFI is the elimination of fructose from the diet. Once the patient no longer ingests fructose, sucrose, or sorbitol, clinical symptoms resolve.

6.4.5 Diabetes Mellitus

Hyperosmolar nonketotic diabetic coma (HHNC) is a syndrome of acute deterioration of diabetes mellitus, occurring mainly in the elderly and characterized by marked hyperglycemia, hyperosmolarity, severe dehydration, occasional neurological signs, decreased alertness, and absence of ketonemia or acidosis.

Diabetes mellitus (DM) is the metabolic disease characterized by hyperglycemia (elevated blood glucose levels) which may rise upto 500mg%. You know that insulin is released by the β -cells of pancreas in response to high blood glucose levels such as after taking meals rich in sugars, that signals changes in metabolic pathways so that glucose levels are brought to normal levels. Diabetes is seen when either there is insufficient secretion of insulin by pancreas cells do not respond to insulin produced by the pancreatic cells. Based on the underlying etiology, DM is clinically classified into Type 1 DM and Type 2 DM. High blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). Let us learn more about different types of DM.

Type 1 DM, also known as insulin dependent diabetes mellitus (IDDM) or juvenile diabetes. It results from the failure of pancreas to produce sufficient insulin due to destruction of insulin producing cells. Therefore, the patient is treated with exogenous introduction of insulin through insulin injection. This diabetes occurs more frequently in children and young people (till 30 years).

Type 2 DM, also referred to as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes is due to insulin resistance. It means insulin is produced but cells are not able to respond to it or utilize it properly. This type of DM is managed with the changes in diet and lifestyle (exercise) and non-insulin antihyperglycemic medicines such as metformin, if needed. Table 6.2 provides a comparative overview of both types of DM.

Both types of DM are chronic diseases which cannot be cured but managed by the drugs. As we learnt in the beginning the importance of glucose homeostasis, therefore, untreated diabetes is associated with many complications. Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma. Serious long-term complications include cardiovascular disease, chronic renal failure, and diabetic retinopathy (retinal damage). Adequate treatment of diabetes with appropriate drugs, as well as blood pressure control and lifestyle factors such as stopping smoking and maintaining a healthy body weight is important.

Table 6.2: General characteristics of Type I and Type II Diabetes mellitus

Characteristic	DM Type I	DM Type II
Plasma level of endogenous insulin	Extremely low to undetectable	Low or elevated depending on the degree of insulin resistance and insulin secretory defect
Pancreatic autoantibodies at diagnosis	Yes	No
Pathology of islets of Langerhans	Insulinitis, selective loss of most beta cells	Smaller, normal appearing islets, amyloid deposition
Age at onset	Most commonly <30 years	Most commonly >30 years
Associated Obesity	Uncommon	Very common
Insulin treatment required for control of ketoacidosis	Yes	No
Prone to diabetic complications (neuropathy, retinopathy, nephropathy, CVD, atherosclerosis)	Yes	Yes
Hypoglycemia responsive to non-insulin antiglycemic medicines	No	Yes, initially in many patients

Risk factors of DM include but not restricted to obesity, family history of diabetes, sedentary lifestyle, smoking and prediabetic condition. DM is also induced following some viral infections such as measles, viral hepatitis or autoimmune diseases such as thyroid gland (autoimmune thyroiditis, diffuse toxic goitre) and adrenal gland (Addison's disease).

Gestational diabetes occurs in some women during pregnancy as their body can't make the extra insulin needed during pregnancy. Hormonal changes during pregnancy can make it harder for blood glucose to enter the causing insulin resistance.

Cardiovascular complication, neuropathy, retinopathy and kidney failure are some of the complications associated with long term and uncontrolled diabetes.

Primary diagnosis of diabetes is based on determination of either fasting plasma glucose (FPG) levels or oral glucose tolerance test (OGTT) or HbA1C level.

Table 6.3 gives the relation between these values with diagnosis of diabetes.

In practice, diabetes mellitus or impaired fasting glucose regulation is often diagnosed using random measures of plasma glucose or of HbA1C. A random glucose value > 200 mg/dL (> 11.1 mmol/L) may be diagnostic, but values can be affected by recent meals and must be confirmed by repeat testing; however, in the presence of symptoms of diabetes, testing twice may be not be necessary.

Table 6.3: Diagnostic criteria of Diabetes mellitus and impaired glucose regulation

Test	Normal	Impaired glucose regulation	Diabetes
Fasting plasma glucose (mg/dL) [mmol/L]	<100 [<5.6]	100-125 [5.6-6.9]	≥126 [≥ 7.0]
Oral Glucose tolerance test (mg/dL) [mmol/L]	<140 [<7.8]	140-199 [7.8-11.0]	≥ 200 [≥ 11.1]
HbA1c	< 5.7	5.7- 6.4	≥ 6.5
Random glucose (mg/dL) [mmol/L]	<200 [<11.1]	-	> 200 [>11.1] in patients with symptoms

HbA1C is also known as glycated haemoglobin. During circulation, sugars get chemically attached to haemoglobin, giving it the name glycated hemoglobin. HbA1C increases with blood glucose and has a validated relationship with average glucose level over the preceding 3 months (as average half-life of RBCs is 120 days). Following conclusion about diabetic status of a person may be drawn from the HbA1C measurements:

HbA1C ≥ 6.5% = diabetes

HbA1C 5.7 to 6.4% = prediabetes or at risk of diabetes

As HbA1C is an indirect measure of blood glucose; values may be falsely high or low and can vary with race/ethnicity. Tests must be done in a certified

clinical laboratory with an assay that is certified and standardized to a reference assay.

While FPG involves taking blood sample after 8-10 hours of overnight fasting before determination of blood /plasma glucose; in OGTT after overnight fasting, the patient is made to drink a solution equivalent to 75 g of glucose. Basal blood sugar is noted at time point 0 and is again determined after 2 hours. OGTT is more sensitive test for diagnosing border line diabetes and impaired glucose tolerance, but is less convenient and reproducible than FPG. It is therefore rarely used routinely, except for diagnosing gestational diabetes and for research purposes.

Urine glucose measurement, once commonly used, is no longer used for diagnosis or monitoring because it is neither sensitive nor specific.

SAQ 2

- a) Draw Leloir pathway beginning from galactose.
 - b) What are full forms of GALK, GALT and GALE?
 - c) Which enzyme is deficient in Pompe disease?
 - d) Name the disorder characterized by increased levels of xylulose in urine.
 - e) Which of the two DMI or DM II is due to insulin resistance and is seen to develop after 30 years of age?
 - f) How are HbA1c values used as diagnostic test for diabetic status of an individual?
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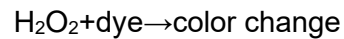
6.5 MEASUREMENT OF BLOOD AND URINE GLUCOSE LEVELS

Dipstick and glucometer are commonly used devices for quick determination of glucose levels in blood, plasma or urine. Both these devices measure glucose use the same method known as Glucose oxidase- peroxidase method.

6.5.1 GOP-POD Method

Glucose oxidase- peroxidase method uses two coupled enzymatic reactions to measure the presence of glucose. The first reaction uses the enzyme glucose oxidase to oxidize the glucose, forming gluconic acid and hydrogen peroxide. The second reaction uses the hydrogen peroxide to oxidize a dye to form a coloured product, or chromogen. The coloured product can be visually observed or measured by an instrument. The amount of coloured product formed is proportional to the amount of glucose present in the urine.

The reactions are as follows:



6.5.2 Glucometer

A portable device used by diabetic individuals to monitor their blood glucose levels at home is glucometer, also known as a glucose meter (Fig.6.6). It provides immediate feedback, allowing informed decisions on diet, medication, and health. By pricking the skin and placing blood on a test strip, the device measures blood sugar levels digitally. When blood is added to a test strip, the enzyme glucose oxidase catalyses the oxidation of glucose into gluconic acid and hydrogen peroxide.



The amount of hydrogen peroxide produced is directly proportional to the concentration of glucose in the blood sample. This reaction generates an electric current, which is measured by the glucometer. The device then calculates the corresponding blood glucose level based on this current.

6.5.3 Dipstick

The dipstick is a rapid method of determining the presence of urinary glucose, which can be used to screen diabetes or monitor the therapy of diabetics. You might have seen such dipsticks as they are routinely used for urine analysis (Fig. 6.5). Patient is instructed to collect the urine in an appropriate specimen container. The strip is quickly dipped in the urine; excess urine is removed by moving the edge of the strip against the rim of the container. 30 seconds of time is noted beginning as soon as the strip is placed in the urine.



Fig. 6.5: Dipsticks used for urine analysis.

After 30 seconds the colour of the strip is visually matched to the chart colour provided with the pack of dipstick to strip visually to determine the presence or absence of glucose in urine. Commercial instruments in diagnostic laboratories can read the strip automatically and results are printed.

The chromogen formation is visible after a minimal amount is converted. For many dipsticks this is in the range of 75-125 mg/dL of urine. There is also a maximum colour change that can be obtained with the strip reagent. This is commonly set at 2000 mg/dL.

6.6 SUMMARY

Let us summarize what we have learnt so far.

- Major pathways of carbohydrate metabolism include (1) glycolysis, 2) citric acid cycle (TCA cycle), (3) hexose monophosphate shunt (HMP shunt), (4) gluconeogenesis, (5) glycogen metabolism (glycogenolysis and glycogenesis), (6) uronic acid pathway (7) Cori cycle and 8) glucose- alanine cycle. All these metabolic pathways are interconnected.
- Homeostasis or maintenance of glucose levels involves coordinated regulation of various metabolic pathways that contribute to addition and removal of glucose in blood.
- Conditions that disturb glucose homeostasis result in altered blood glucose levels; either hyperglycemia (increase) or hypoglycemia (decrease). These conditions may arise due to inborn errors of metabolism or develop later in life due to environmental factors, unhealthy life style or work-related factors.
- Many diseases arise due to inborn errors of carbohydrate metabolism result from defects at genetic level, consequently either the enzyme is not formed in sufficient amounts or it is not functional. These are galactosemia, glycogen storage diseases, pyruvate carboxylase deficiency, fructose-1,6-bisphosphatase deficiency, hereditary fructose intolerance, pentosuria and glucose-6-phosphate dehydrogenase deficiency.
- Diabetes mellitus occurs due to genetic disposition or wrong life style.
- Galactosemia is a condition in which body is unable to metabolize galactose due to deficiency of any of the enzyme in Leloir pathway.

- Glycogen storage diseases (GSD) are the group of inherited diseases that affect glycogen metabolism. Mutations are found in the genes encoding the enzymes that regulate its processing, leading to abnormal concentrations or structures.
- Essential pentosuria refers to the condition characterized by high levels of a pentose sugar, L-xylulose in urine.
- Essential fructosuria, an inherited disorders of fructose metabolism occurs due to deficiency of fructokinase resulting in elevated levels of fructose in urine and blood. However, this is an asymptomatic disorder and therefore not of clinical significance.
- Another group of disorders is hereditary fructose intolerance (HFI). It is seen in individuals having mutations in gene encoding for the enzyme aldolase B.
- Diabetes mellitus (DM) is the metabolic disease characterized by hyperglycemia (elevated blood glucose levels) which may rise up to 500mg%.
- DM is clinically classified into Type 1 DM and Type 2 DM. High blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger).
- Dipstick and glucometer are commonly used devices for quick determination of glucose levels in blood, plasma or urine. Both these devices measure glucose use the same method known as glucose oxidase- peroxidase method.

6.7 TERMINAL QUESTIONS

1. What is meant by glucose homeostasis? How is it maintained?
2. a) pentosuria b) galactosemia c) diabetes mellitus I
3. What are glycogen storage diseases? List the cause of any three diseases of this group.
4. Explain two devices used for rapid measurement of glucose in blood and urine.

6.8 ANSWERS

Self-Assessment Questions

1. a) 60-100mg/dl and 100-140 mg/dl
b) Insulin; glucagon
2. a) Galactose → Galactose-1-phosphate → UDP- galactose → UDP- glucose
b) GALK -Galactokinase; GALT - galactose-1-phosphate uridylyl transferase; GALE- UDP-galactose-4'-epimerase

- c) Lysosomal acid- α -glucosidase
- d) Pentosuria
- e) DM-II
- f) Normal individual have HbA1c < 5.7, while it ranges from 5.7- 6.4 in impaired glucose regulation. If the value is ≥ 6.5 , the patient is diabetic.

Terminal Questions

1. Maintenance of blood glucose levels within narrow range constitutes glucose homeostasis. Liver plays an important role in it by coordinated regulation of factors contributing to the rate of glucose entry and its removal from blood. Please refer to the section 6.3 for more details.
2.
 - a) Pentosuria: Essential pentosuria is characterized by high levels of a pentose sugar, L-xylulose in urine due to deficiency of enzyme L-xylulose reductase that converts xylulose to xylitol. Despite the excess sugar, affected individuals have no associated health problems. It is a rare disease and occurs almost exclusively in individuals with Ashkenazi Jewish ancestry. Affected, as a result excess sugar is released in urine.

Another type of pentosuria is alimentary pentosuria. It is a genetic disease, is non-inherited which may occur following intake of excessive amounts of fruits high in L-xylulose or another pentose called L-arabinose. However, the condition disappears when diet is changed. Please refer to the section 6.3.3 for more details.
 - b) Galactosemia: Galactosemia is an autosomal recessive hereditary disorder caused by the deficiency of any of the enzyme in Leloir pathway. Refer to section 6.3.1. In this condition, the patient is unable to metabolize galactose.
 - c) Diabetes mellitus I: High blood glucose levels that results from the failure of pancreas to produce sufficient insulin due to destruction of insulin producing cells. section 6.3.4
3. Glycogen storage diseases (GSD) are the group of inherited diseases that affect glycogen metabolism. Mutations are found in the genes encoding the enzymes that regulate its processing, leading to abnormal concentrations or structures. Refer to the section 6.3.2 for its various types.
4. Dipstick and glucometer. Please refer to the section 6.4.2 and 6.4.3 for more details about these devices.



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