# Introduction to
# Carbohydrates Metabolism

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١ . Glucose is the main product of dietary carbohydrate metabolism .The brain is almost entirely dependent on extracellular glucose as an energy source and maintenance of plasma glucose levels is important for normal cerebral function .

٢ . After a carbohydrate - containing meal excess glucose is :

- Stored as glycogen in liver and muscles .
- Converted to fat and stored in adipose tissue .

Insulin stimulates these processes .

٣ . During fasting :

- Glycogen breakdown in the liver ( and kidney ) releases glucose into the plasma .
- Triglycerides breakdown in adipose tissue releases glycerol which can be converted to glucose , and fatty acids which can be metabolized by most tissues other than the brain .

٤ . Muscle glycogen is used to generate ATP for muscle contraction while liver glycogen is used to maintain blood glucose during fasting or exercise .

## Stages of carbohydrates metabolism

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١ . Glycolysis ( Glycolytic pathway )( Emden - Meyerhof pathway )

Can be defined as a sequence of reactions for the breakdown of glucose to two molecules of pyruvic acid under aerobic conditions or lactic acid under anaerobic conditions along with the production of small amount of energy , this occurs in the cytoplasm of all the cells of the body .

$$\text{Glucose} \rightarrow ٢\ \text{Lactate}^- + ٢H^+$$

The lactate is transported in the blood stream to the liver where it can be used for gluconeogenesis , providing further glucose for the muscle ( Cori cycle ) . ( Metformin and phenformin , drugs used for treat diabetes mellitus because they can cause severe lactic acidosis, they inhibit both the TCA cycle and gluconeogenesis ) .

٢ . Kreb's cycle ( Citric acid cycle )(Tri carboxylic acid cycle )

Is a series chemical reactions used by all aerobic organisms to release stored energy through the oxidation of acetyl CoA derived from carbohydrates , fats and proteins into $CO_2$ and ATP . In eukaryotic cells , the CAC occurs in the matrix of the mitochondrion . In prokaryotic cells , such as bacteria , which lack mitochondria , the CAC reaction sequence is performed in the cytosol with the proton gradient for ATP production being across the cells surface ( plasma membrane ) rather than the inner membrane of the mitochondrion .

٣ . Glycogenesis ( anabolic reaction ):

Is the process of glycogen synthesis in which glucose molecules are added to chains of glycogen for storage . This process is activated by insulin in response to high glucose levels .

٤ . Glycogenolysis (catabolic reaction):

Is the breakdown of glycogen to glucose – ١ – phosphate and glycogen $_{(n-1)}$ by the enzyme glycogen phosphorylase in the liver , muscles and the kidney . This process occurs to provide glucose when necessary .

٥ .Gluconeogenesis

Is the process of synthesizing glucose from non-carbohydrate precursors such as lactate , amino acids and glycerol , occurs mainly in the liver and kidneys . It is a particular importance when carbohydrate is not available from the diet .

Gluconeogenesis take place :

* During fasting or starvation or when the level of liver glycogen is low . Gluconeogenesis is important in keeping the blood glucose level .
* During long exercise, lactate is used as precursor.
*When ATP is available in the cell ( or we need minimum energy requirement ) .

Regulation of gluconeogenesis occurs by three hormones :

*Under fasting conditions , glucagon is elevated and stimulates gluconeogenesis ( gluconeogenesis is stimulate in starvation ) .

*Gluconeogenesis is inhibited by insulin and after CHO feeding .

*Glucocorticoids are steroid hormones stimulates gluconeogenesis .

٦ . Other pathway such as pentose phosphate pathway for production of ribose and NADPH .

## Sources of blood glucose

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١ . From CHO in the diet :

Most CHO in the diet form glucose , galactose and fructose . Upon digestion , these are absorbed into the portal vein . In the liver , fructose and galactose are converted into intermediates in the pathway by which glucose is metabolized .

٢ . From glucogenic compounds that undergo through gluconeogenesis :

A–Compounds that directly convert into glucose without significant recycling e.g. amino acids such as alanine .

B – Compounds that are products of the partial metabolism of glucose in certain tissues and move to liver and kidney to resynthesize glucose e.g. lactate formed in skeletal muscle convert to glucose in Cori cycle .

٣ . From liver glycogen by glycogenolysis .

## Utilization of blood glucose

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١ . Formation of glycogen in the liver ( glycogenesis ) .

٢ . Formation of glycogen in the muscles and adipose tissues .

٣ . The liver can convert some of the excess glucose to fatty acids , which are ultimately transported as triglyceride in very low density lipoprotein ( VLDL ) and stored in adipose tissue .
٤ . Oxidation to supply energy ( glycolysis ) .
٥ . Synthesis of glycolipids , glycoproteins , lactose and nucleic acids .
٦ . Extraction in the urine when blood glucose level exceeds renal threshold ( abnormal ) . If plasma glucose levels exceed about ١١ mmol / liter ( ١٩٠ mg / dl ) and renal function is normal , glycosuria will be present ( high urinary glucose concentrations produce an osmotic diuresis and therefore polyuria ) ( Glycosuria is the excretion of glucose into the urine , ordinarily , urine contains no glucose because the kidneys are able to reabsorb all of the filtered glucose from the tubular fluid back into the bloodstream ) .

## Phosphorylation of blood glucose

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Glucose is phosphorylated to glucose-٦-phosphate in a reaction that is common to the first reaction in the pathway of glycolysis from glucose .The reaction is catalyzed by :

A . Hexokinase :

It is found in most tissues and is geared to provide glucose -٦- phosphate for ATP production even when blood glucose is low .

a – Hexokinase has a low Km for glucose (about ٠.١ mM) . Therefore , it is working near its maximum rate ( Vmax. ) even at fasting blood glucose levels .

b – Hexokinase is inhibited by its product , G-٦-P . Therefore it is most active when G-٦-P is being rapidly utilized .

B – Glucokinase : It is specific for glucose sugar , is found in the liver .

a – Glucokinase has a high Km for glucose ( about ٦ mM ) . Therefore it is very active after a meal when glucose levels in the hepatic portal vein are high , and it is relatively inactive during fasting when glucose levels are low .

b – It is not inhibited by its product , G-٦-P .

When glucose enters cells , it is converted to G-٦-P,which is a pivotal compound in several metabolic pathways :

* The major fate of G-٦-P is to enter the pathway of glycolysis , which produce pyruvate and generates NADH and ATP .

* G-٦-P can be converted to G-١-P and then to UDP– glucose , which is used for the synthesis of glycogen .

* G-٦-P can also enter the pentose phosphate pathway , which produces NADPH and ribose for nucleotide production .

The conversion of glucose to G٦P , the first step in glucose metabolism in all cells , is catalyzed in the liver by the enzyme glucokinase , which has a low affinity for glucose compared with that of hexokinase found in most other tissues . Glucokinase activity is induced by insulin .
The function of insulin is to increase the entrance of glucose into the cell by stimulating the reaction of conversion ( G → G٦P ) , thus if insulin is not present , then glucose will not be converted into G٦P and cannot enter the cell , while it remains in blood and causes diabetic .

Insulin ↓
Glucose ----------> G٦P
↓
Glucose increase in blood
Glucose decrease in tissues
↓
Diabetes

## Common problems associated with carbohydrates metabolism

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١ . Intestinal lactase deficiency :

Intestinal lactase deficiency is a common condition in which lactose cannot be digested and it oxidized by bacteria in the gut , which produce gas and causing bloating and watery diarrhea .

٢ . Hypoglycemia ( low blood sugar ) :

Is caused by the inability of the liver to maintain blood glucose levels ( occurs if the plasma glucose level is less than ٤٥ mg / dl ). Hypoglycemia occurs during prolonged fasting , insulinoma ( is a primary tumour of the islet cells of the pancreas ) , impaired liver function and excessive alcohol ingestion ( metabolism of alcohol increase levels of NADH in the liver , which inhibit gluconeogenesis ) .

٣ . Diabetes mellitus :

Is the result of relative or absolute insulin deficiency . ( Type ١ , or insulin – dependent diabetes mellitus , IDDM , results from the pancreases failure to produce enough insulin ) ( Type ٢ , or noninsulin–dependent diabetes mellitus , NIDDM , begins with insulin resistance ) .

Diabetes associated with other conditions includes :

- Absolute insulin deficiency , due to the pancreatic disease { chronic pancreatitis , haemochromatosis ( iron deposition in the liver may cause cirrhosis ) , cystic fibrosis } .
- Relative insulin deficiency , due to the excessive growth hormone ( acromegaly ) or glucocorticoid levels due to administration of steroids .
- Drugs , such as thiazide diuretics .

٤. Galactosemia :

The appearance of high concentrations of galactose in the blood after lactose ingestion may be due to the galactokinase deficiency . In this conditions , galactose

accumulates and is reduced to galactitol , which causes cataracts .

## Notes :

١ . The reaction of the phosphorylation is irreversible because the energy in glucose and ATP is higher than the energy in G٦P , so there is loss of energy and reaction goes forward only .

٢ . The plasma glucose concentration depends on the balance between glucose entering and glucose leaving the extracellular compartment . The maintenance of blood glucose is a major function of the liver .

٣ . Muscle glycogen cannot provide blood glucose by glycogenolysis due to lacks of the enzyme ( glucose - ٦ - phosphatase ) . Because of the absence of these enzyme , this glycogen cannot be reconverted to glucose and can only supply necessary energy .

٤ . How to determine whether you have diabetes , prediabetes or neither : there are three possible tests :

a – The HbA١c test :
- At least ٦.٥ % means diabetes .
- Between ٥.٧ % and ٥.٩٩ % means prediabetes .
- Less than ٥.٧ % means normal .

b – The FPG ( fasting plasma glucose ) test :
- At least ١٢٦ mg / dl means diabetes .
- Between ١٠٠ mg / dl and ١٢٥.٩٩ mg / dl means prediabetes .
- Less than ١٠٠ mg / dl means normal .

c – The OGTT ( oral glucose tolerance test ) :
- At least ٢٠٠ mg / dl means diabetes .
- Between ١٤٠ mg / dl and ١٩٩.٩ mg / dl means prediabetes .
- Less than ١٤٠ mg / dl means normal .

٥ . Regulation of glycogen metabolism occurs by three hormones : epinephrine , glucagon and insulin .

٦ . Hyperglycemia occurs :
- In the syndrome of diabetes mellitus .
- In patients receiving intravenous glucose – containing fluids .
- Temporarily in severe stress .
- Sometimes after cerebrovascular accidents ( CVA ) .

٧ . The aldehyde or ketone group of a sugar can reduced to a hydroxyl group , forming a polyol ( glucose is reduced to sorbitol and galactose to galactitol by the enzyme aldose reductase ) .

٨ . Even after ٥ – ٦ weeks of starvation , blood glucose levels are still in the range of ٦٥ mg / dl .

٩ . During the first trimester of pregnancy , the HbA١c target for women with diabetes is the same as for planning a pregnancy , that is ٦.١ % or lower .
During the second and third trimesters of pregnancy , from week ١٣ onwards , HbA١c should not be used for assessing blood glucose control .
Throughout pregnancy , women with diabetes should aim to meet the following blood glucose targets :
Before meals : ٣.٥ to ٥.٩ mmol / l .
١hour after meals : ٧.٨ mmol / l or under .

١٠ . HbA١c is not used for diagnosing gestational diabetes .
Pregnant women without diabetes will be screened for possible gestational diabetes between weeks ٨ and ١٢
of the pregnancy and an OGTT will be carried out between weeks ٢٤ and ٢٨ .
If you have had gestational diabetes during a previous pregnancy , you will be given an OGTT between ١٦ and

١٨ weeks and then at ٢٨ weeks .