Unit One

Chemistry of Carbohydrates

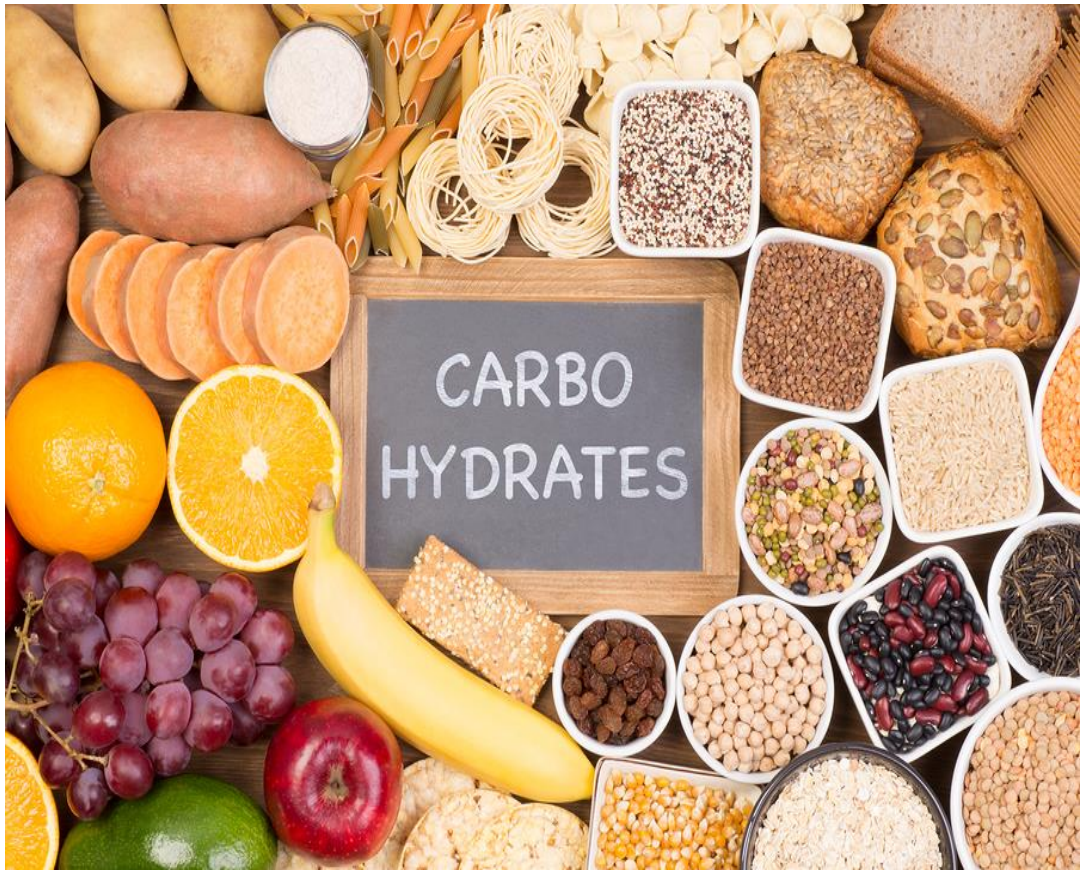
Assist. Lec. Sadoun Abbas Alsalimi
Department of Basic Sciences
College of Nursing
University of Basrah

Unit 1. Chemistry of Carbohydrates

Definition of Carbohydrates

Carbohydrates are organic substances containing C, H and O. Hydrogen atoms are present usually in the ratio of 2:1 as it occurs in a water molecule. *Example:* glucose, fructose, lactose, starch, etc. There may be exception to the above, e.g. $C_2H_4O_2$ is acetic acid and not a carbohydrate though H and O are in the ratio of 2:1.

Carbohydrates are defined chemically as aldehyde or ketone derivatives of the higher polyhydric alcohols or compounds which yield these derivatives on hydrolysis.



Unit 1. Chemistry of Carbohydrates

Classification of Carbohydrates

Carbohydrates are classified into **four** major groups:

1- ***Monosaccharide (simple sugars):*** They cannot be hydrolyzed into simpler forms.

2- ***Disaccharides:*** They yield two molecules of same or different monosaccharide units on hydrolysis.

3- ***Oligosaccharides:*** They yield three to six molecules of monosaccharides on hydrolysis.

4- ***Polysaccharides (Glycans):*** They yield more than 6 molecules of monosaccharides on hydrolysis.

** **Monosaccharides** are further classified into **two** groups depending on:

1- The number of carbon atoms they possess, e.g. trioses (3), tetroses (4), pentoses (5), hexoses (6), etc.

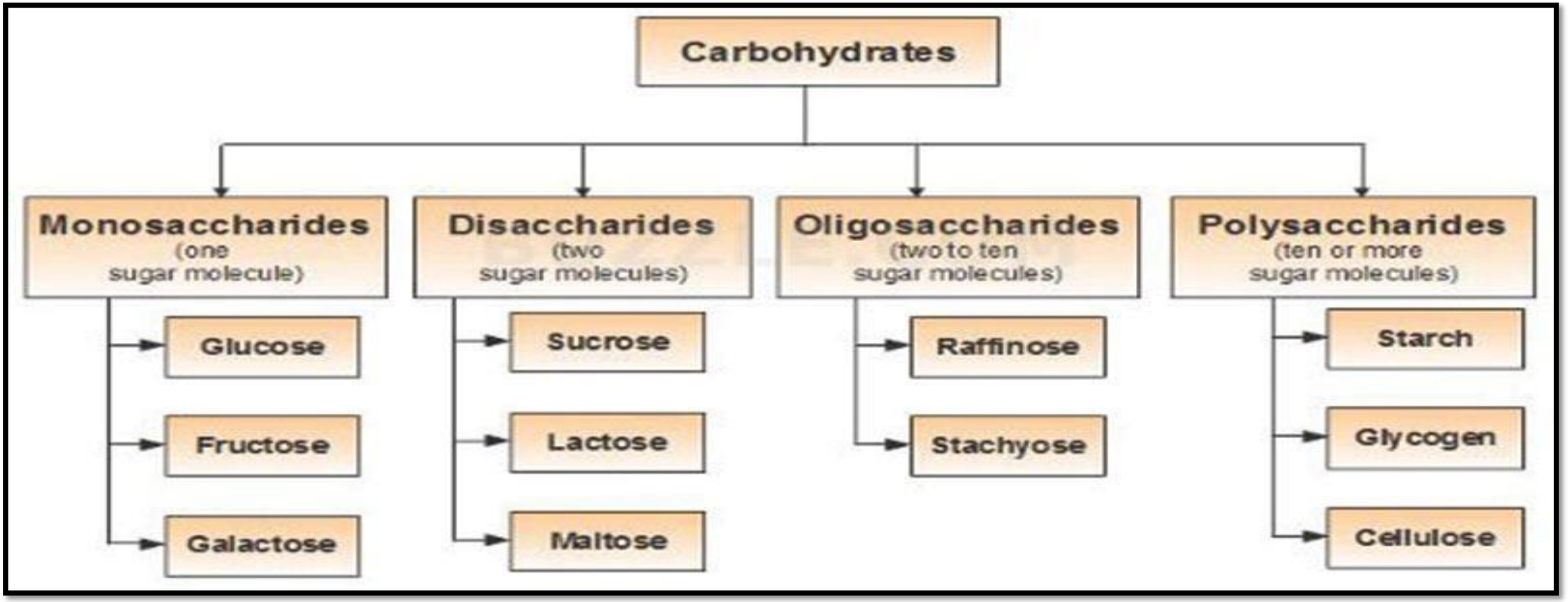
2- Whether aldehyde (-CHO) or ketone (-CO) group is present, e.g. aldoses, ketoses.

** **Polysaccharides** are classified into **two** main groups:

1- ***Homopolysaccharides (hemoglycans):*** Polymer of same monosaccharide units, e.g. starch, glycogen, insulin, dextrins, cellulose, etc.

2- ***Heteropolysaccharides (heteroglycans):*** Polymer of different monosaccharide units or their derivatives, e.g. mucopolysaccharides (MPS).

Unit 1. Chemistry of Carbohydrates



Schematic demonstrates Classification of Carbohydrates

Unit 1. Chemistry of Carbohydrates

Properties of Carbohydrates

The physical, chemical, and biological properties of carbohydrates depend on their primary structures and on their higher-order structures.

Chemical Properties of Carbohydrates

The chemical properties of carbohydrates depend on the monosaccharide residues present, their functional groups, the linkage position(s) and configurations. In spite of the unique properties of each molecular entity, some general chemical properties can be ascribed to carbohydrates:

1- Hydrolysis/Dissolving.

2- Oxidation/Reduction.

3- Functional Groups.

4- Chelation and Complexation.

Unit 1. Chemistry of Carbohydrates

Metabolism of Carbohydrates

This section will discusses carbohydrate metabolism and its abnormalities, with emphasis on diabetes mellitus and hypoglycaemia. In the next decade it is predicted that there will be about 250 million people worldwide with type 2 diabetes mellitus.

1- Chemistry of Carbohydrates

The main monosaccharide hexoses are reducing sugars. Naturally occurring polysaccharides are long-chain carbohydrates composed of glucose subunits:

1- Starch: found in plants, is a mixture of amylose (straight chains) and amylopectin (branched chains).

2- Glycogen: found in animal tissue, is a highly branched polysaccharide.

Unit 1. Chemistry of Carbohydrates

2- Functions of Extracellular Glucose:

The main function of glucose is as a major tissue energy source. The brain is highly dependent upon the extracellular glucose concentration for its energy supply; indeed, hypoglycaemia is likely to impair cerebral function or even lead to irreversible neuronal damage. This is because the brain cannot:

(1) synthesize glucose.
(2) store glucose in significant amounts.
(3) metabolize substrates other than glucose and ketones (plasma ketone concentrations are usually very low and ketones are of little importance as an energy source under physiological conditions).
(4) extract enough glucose from the extracellular fluid (ECF) at low concentrations for its metabolic needs, because entry into brain cells is not facilitated by insulin.

Normally the plasma glucose concentration remains between about 4-10 mmol/L, despite the intermittent load entering the body from the diet. The maintenance of plasma glucose concentrations below about 10 mmol/L minimizes loss from the body as well as providing the optimal supply to the tissues. Renal tubular cells reabsorb almost all the glucose filtered by the glomeruli, and urinary glucose concentration is normally too low to be detected by the usual tests, even after a carbohydrate meal. Significant glycosuria usually occurs only if the plasma glucose concentration exceeds about 10 mmol/L (the renal threshold).

Unit 1. Chemistry of Carbohydrates

3- Important Terms in Carbohydrates Metabolism:

(1) Glycogenesis: is the process of glycogen synthesis, in which glucose molecules are added to chains of glycogen for storage. This process is activated in the liver during rest periods following the Cori cycle and also activated by insulin in response to high glucose levels.

(2) Glycogenolysis: is the breakdown of glycogen (n) to glucose and glycogen (n-1). Glycogen branches are catabolized by the sequential removal of glucose monomers via phosphorolysis by the enzyme glycogen phosphorylase.

(3) Glycolysis: is the metabolic pathway that converts glucose, into pyruvate (pyruvic acid) and a hydrogen ion. The free energy released in this process is used to form the high-energy molecules ATP (adenosine triphosphate) and NADH (reduced nicotinamide adenine dinucleotide). Glycolysis is a sequence of ten enzyme-catalyzed reactions. Most monosaccharides, such as fructose and galactose, can be converted to one of these intermediates.

(4) Kreb's Cycle: it is called also the citric acid cycle (CAC) or tricarboxylic acid cycle (TCA cycle) which is a series of chemical reactions used by all aerobic organisms to release stored energy through the oxidation of acetyl-CoA derived from carbohydrates, fats, and proteins. In addition, the cycle provides precursors of certain amino acids, as well as the reducing agent NADH, that are used in numerous other reactions. Its central importance to many biochemical pathways suggests that it was one of the earliest components of metabolism and may have originated abiogenically. Even though it is branded as a 'cycle', it is not necessary for metabolites to follow only one specific route; at least three segments of the citric acid cycle have been recognized.

Unit 1. Chemistry of Carbohydrates

4- Maintaining Extracellular Glucose Concentrations

A- Control of Plasma Glucose Concentration

During normal metabolism, little glucose is lost unchanged from the body. Maintenance of plasma glucose concentrations within the relatively narrow range of 4–10 mmol/L, despite the widely varying input from the diet, depends on the balance between the glucose entering cells from the ECF and that leaving them into this compartment.

Unit 1. Chemistry of Carbohydrates

B- Hormones Concerned with Glucose Homeostasis:

1- **Insulin**: Insulin is the most important hormone controlling plasma glucose concentrations. A plasma glucose concentration of greater than about 5 mmol/L stimulates insulin release from the pancreas beta-cells. Insulin binds to specific cell surface receptors on muscle and adipose tissue, thus enhancing the rate of glucose entry into these cells. Insulin-induced activation of enzymes stimulates glucose incorporation into glycogen (glycogenesis) in liver and muscle. Insulin also inhibits the production of glucose (gluconeogenesis) from fats and amino acids, partly by inhibiting fat and protein breakdown (lipolysis and proteolysis). The transport of glucose into liver cells is insulin independent but, by reducing the intracellular glucose concentration, insulin does indirectly promote the passive diffusion of glucose into them. Insulin also directly increases the transport of amino acids, potassium and phosphate into cells, especially muscle; these processes are independent of glucose transport. In the longer term, insulin regulates growth and development and the expression of certain genes.

Unit 1. Chemistry of Carbohydrates

2- **Glucagon:** Glucagon is a single-chain polypeptide synthesized by the alpha-cells of the pancreatic islets. Its secretion is stimulated by hypoglycaemia. Glucagon enhances hepatic glycogenolysis (glycogen breakdown) and gluconeogenesis.

3- **Somatostatin:** This peptide hormone is released from the D cells of the pancreas and inhibits insulin and growth hormone release.

4- **Other hormones:** When plasma insulin concentrations are low, for example during fasting, the hyperglycaemic actions of hormones, such as growth hormone (GH), glucocorticoids, adrenaline (epinephrine) and glucagon, become apparent, even if there is no increase in secretion rates. Secretion of these so-called counter regulatory hormones may increase during stress and in patients with acromegaly, Cushing's syndrome and phaeochromocytoma and thus oppose the normal action of insulin.

Unit 1. Chemistry of Carbohydrates

C- The Liver

The liver is the most important organ maintaining a constant glucose supply for other tissues, including the brain. It is also of importance in controlling the postprandial plasma glucose concentration. Portal venous blood leaving the absorptive area of the intestinal wall reaches the liver first, and consequently the hepatic cells are in a key position to buffer the hyperglycaemic effect of a high-carbohydrate meal. The entry of glucose into liver and cerebral cells is not directly affected by insulin, but depends on the extracellular glucose concentration. The conversion of glucose to (G6P), the first step in glucose metabolism in all cells, is catalyzed in the liver by the enzyme glucokinase. Glucokinase activity is induced by insulin. Therefore, hepatic cells extract proportionally less glucose during fasting, when concentrations in portal venous plasma are low, than after carbohydrate ingestion. This helps to maintain a fasting supply of glucose to vulnerable tissues such as the brain. The liver cells can store some of the excess glucose as glycogen. The rate of glycogen synthesis (glycogenesis) from G6P may be increased by insulin secreted by the beta-cells of the pancreas in response to systemic hyperglycaemia. 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.

Unit 1. Chemistry of Carbohydrates

** Under normal aerobic conditions, the liver can synthesize glucose by gluconeogenesis using the metabolic products from other tissues, such as glycerol, lactate or the carbon chains resulting from deamination of certain amino acids (mainly alanine). The liver contains the enzyme glucose-6-phosphatase, which, by hydrolysing G6P derived from either glycogenolysis or gluconeogenesis, releases glucose and helps to maintain extracellular fasting concentrations. Hepatic glycogenolysis is stimulated by the hormone glucagon, secreted by the alpha-cells of the pancreas in response to a fall in the plasma glucose concentration, and by catecholamines such as adrenaline or noradrenaline. During fasting, the liver converts fatty acids, released from adipose tissue as a consequence of low insulin activity, to ketones. The carbon chains of some amino acids may also be converted to ketones. Ketones can be used by other tissues, including the brain, as an energy source when plasma glucose concentrations are low.

Unit 1. Chemistry of Carbohydrates

D- Other Organs

The renal cortex is the only other tissue capable of gluconeogenesis, and of converting G6P to glucose. The gluconeogenic capacity of the kidney is particularly important in hydrogen ion homeostasis and during prolonged fasting. Other tissues, such as muscle, can store glycogen but, because they do not contain glucose-6-phosphatase, they cannot release glucose from cells and so can only use it locally; this glycogen plays no part in maintaining the plasma glucose concentration.

E- Systemic Effects of Glucose Intake:

The liver modifies the potential hyperglycaemic effect of a high-carbohydrate meal by extracting relatively more glucose than in the fasting state from the portal plasma. However, some glucose pass through the liver and the rise in the systemic concentration stimulates the beta-cells of the pancreas to secrete insulin. Insulin may further enhance hepatic and muscle glycogenesis. More importantly, entry of glucose into adipose tissue and muscle cells, unlike that into liver and brain, is stimulated by insulin and, under physiological conditions, the plasma glucose concentration falls to near fasting levels. Conversion of intracellular glucose to G6P in adipose and muscle cells is catalysed by the enzyme hexokinase. The relatively high insulin activity after a meal also inhibits the breakdown of triglyceride (lipolysis) and protein (proteolysis). If there is relative or absolute insulin deficiency, as in diabetes mellitus, these actions are impaired. Both muscle and adipose tissue store the excess post-prandial glucose, but the mode of storage and the function of the two types of cell are very different, as will be shown later.

Unit 1. Chemistry of Carbohydrates

Hyperglycemia & Diabetes Mellitus

Hyperglycemia

Hyperglycaemia is an increase in blood glucose level and it may be due to:

1- intravenous infusion of glucose-containing fluids.

2- severe stress (usually a transient effect) such as trauma, myocardial infarction or cerebrovascular accidents.

3- diabetes mellitus or impaired glucose regulation.

Unit 1. Chemistry of Carbohydrates

Diabetes Mellitus (DM)

The term diabetes mellitus (DM) describes a metabolic disorder of multiple etiologies and it is a group of metabolic diseases in which a person has a high blood sugar, either because the pancreas does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). DM is characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein. These include processes which destroy the beta cells of the pancreas with consequent insulin deficiency, and others that result in resistance to insulin action. The abnormalities of carbohydrate, fat and protein metabolism are due to deficient action of insulin on target tissues resulting from insensitivity or lack of insulin.

Unit 1. Chemistry of Carbohydrates

Classification of Diabetes Mellitus (DM)

1- Type 1 Diabetes Mellitus (T1DM): it results from the deficiency of insulin secretion from β-cells of pancreas, and currently requires the person to inject insulin or wear an insulin pump. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes".

2- Type 2 Diabetes Mellitus (T2DM): it results from insulin resistance (IR), a condition in which cells fail to use insulin properly, and sometimes combined with an absolute insulin deficiency. This form was previously referred to as non-insulin dependent diabetes mellitus (NIDDM) or "adult-onset diabetes".

3- Hybrid Forms of Diabetes.

4- Other Specific Types of Diabetes.

5- Unclassified Diabetes.

6- Hyperglycaemia First Detected During Pregnancy: this type includes two categories of hyperglycaemia when first recognized in pregnancy. One is diabetes mellitus, defined by the same criteria as in non-pregnant persons. The other is gestational diabetes, defined by newly recommended glucose cut-off points that are lower than those for diabetes.

Unit 1. Chemistry of Carbohydrates

** DM is characterized by recurrent or persistent hyperglycemia and is diagnosed by demonstrating any one of the following:

1- Fasting plasma glucose level ≥ 7.0 mmol/L (126 mg/dL).

2- Plasma glucose ≥ 11.1 mmol/L (200 mg/dL) 2hours after a 75 g oral glucose load as in a glucose tolerance test (GTT).

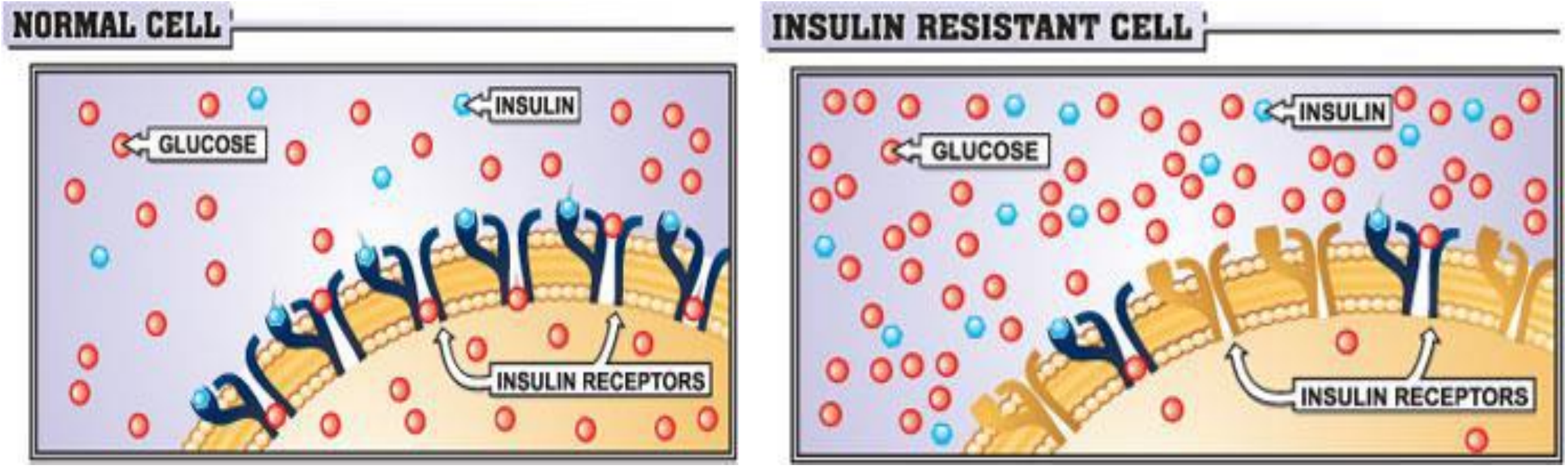
3- Glycated hemoglobin (Hb A1c) ≥ 6.5 %.

A positive result, in the absence of unequivocal hyperglycemia, should be confirmed by a repeat of any of the above methods on a different day. It is preferable to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal GTT, which takes two hours to complete and offers no prognostic advantage over the fasting test. According to the current definition, two fasting glucose measurements above 126 mg/dL (7.0 mmol/L) are considered diagnostic for diabetes mellitus. People with fasting glucose levels from 110 to 125 mg/dL (6.1 to 6.9 mmol/L) are considered to have impaired fasting glucose. Patients with plasma glucose at or above 140 mg/dL (7.8 mmol/L), but not over 200 mg/dL (11.1 mmol/L), two hours after a 75g oral glucose load are considered to have impaired glucose tolerance.

Unit 1. Chemistry of Carbohydrates

Insulin Resistance (IR)

Insulin resistance (IR) is the reducing of biological effects (glucose intake) in tissues and organs to the response for insulin action on the specific cell receptors.



Unit 1. Chemistry of Carbohydrates

Diabetic Complications

DM is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Diabetes as a chronic condition requires careful control. Without proper control and follow-up management, it can lead to various complications. These complications may be divided to short- and long-term complications:

1- Short-Term Complications:

It is acute metabolic complications manifested by increased lipolysis with fatty acid release and accumulation of fat in parenchymal organs further aggravates the metabolic disturbance such as Diabetic Keto Acidosis (DKA), Hyperosmolar Nonketotic States (HNS), Hypoglycemia and Infections.

Unit 1. Chemistry of Carbohydrates

2- Long-Term Complications: :

Many patients with T2DM are asymptomatic, and their disease is undiagnosed for many years. The kidney plays a pivotal role in myocardial failure. Therefore, interfering with the cardio-renal axis is an important therapeutic objective. The duration and intensity of high blood glucose level play an important role in glycosylation of proteins and lead to changes in the shape of the endothelial cells. Lining of the blood vessels, glycoprotein formation and basement membrane become thickening and weak.

The long-term complications of DM can be divided into micro-vascular (damage to small blood vessels) and macro-vascular (damage the arteries) diseases:

Unit 1. Chemistry of Carbohydrates

A- Microvascular Complications:

These are diabetic complications involving small vessels such as the capillaries. Prolonged and chronic high serum glucose plays the central role in the initiation of this condition. There are three major kinds of these Complications: Diabetic Nephropathy (DN), Diabetic Neuropathy (DNu) and Diabetic Retinopathy (DR).

B- Macrovascular Complications:

These are diabetic complications peculiar to large vessels such as arteries and vein. Arteriosclerosis is the main pathological mechanism for developing complications in these vessels. There are three major kinds of these Complications: Cardiovascular Diseases (CVD), Cerebrovascular Diseases (Stroke) and Peripheral Artery Diseases (PAD).

Unit 1. Chemistry of Carbohydrates

Principles of Management of DM

The management of DM is considered briefly, although consulting a specialist text is recommended if further information is required. Insulin requirements vary in patients with type 1 diabetes. For example, the dose may need to be increased during any illness or during pregnancy and reduced if there is increased activity or meals are missed. In patients with type 2 diabetes, plasma glucose concentrations may be controlled by diet, associated with weight reduction, and increased physical activity, but insulin may be required during periods of stress or pregnancy. In this group insulin secretion can be stimulated by the sulphonylurea drugs. Metformin can also be used and are particularly useful in obese patients. Metformin decreases intestinal glucose absorption and hepatic gluconeogenesis as well as increasing tissue insulin sensitivity.. Repaglinide is a meglitinide that increases insulin release from pancreatic beta-cells and enhances tissue insulin sensitivity. The incretins are gastrointestinal hormones that increase insulin release from the pancreas after eating.