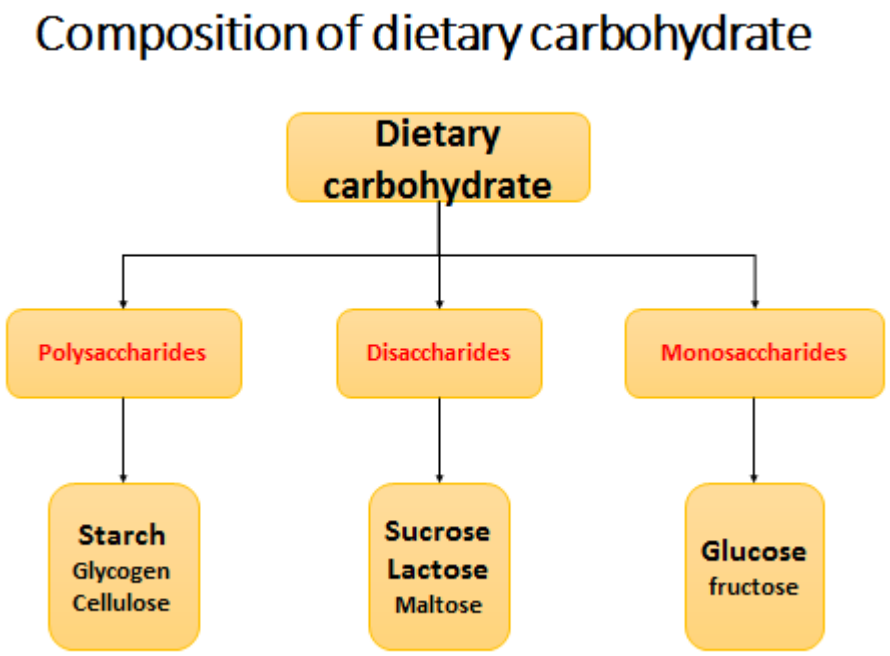
Carbohydrate metabolism and its Regulation

CHEMISTRY OF CARBOHYDRATES

Carbohydrates are aldehyde or ketone derivatives of poly hydroxy (more than one —OH group) alcohols, or compounds that yield these derivatives on hydrolysis. The term *carbohydrate* refers to hydrates of carbon and is derived from the observation that empirical formulas for these compounds contain approximately one molecule of water per carbon atom. Thus glucose, $C_6H_{12}O_6$, and lactose, $C_{12}H_{22}O_{11}$, can be written as $C_6(H_2O)_6$ and $C_{12}(H_2O)$ 11, respectively. These compounds are not hydrates in the usual chemical sense, however, and non-carbohydrate compounds, such as lactic acid, $CH_3CH(OH)COOH$ or $C_3(H_2O)_3$, can have similar empirical formulas.



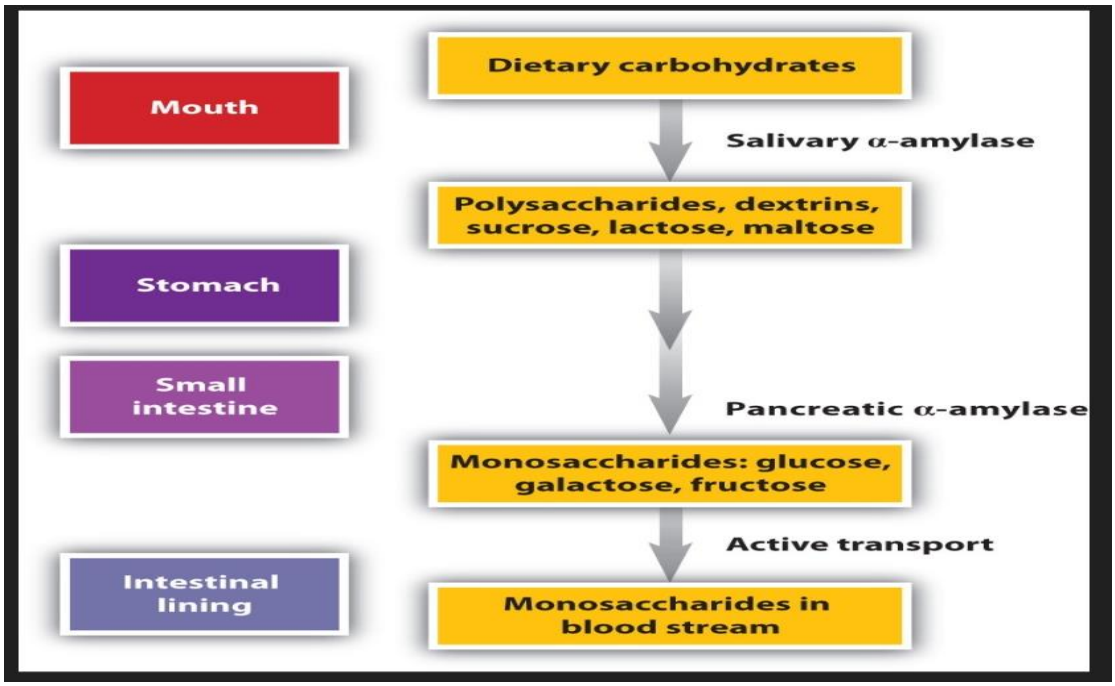
METABOLISM OF CARBOHYDRATES

Carbohydrate metabolism provides glucose, a major energy source for the human body. After digestion of carbohydrates and absorption of glucose, blood glucose concentration is controlled by the action of several hormones. Glucose is synthesized de novo or stored in the tissue as glycogen.

Digestion and Absorption

Ingested starch and glycogen are partially digested by the action of salivary amylase in the mouth to form intermediate dextrins and maltose. The acid pH of the stomach inhibits amylase activity, but alkaline pancreatic secretions increase the pH in the small intestine, allowing pancreatic amylase to complete digestion to oligosaccharides, preponderantly maltose. Maltose, along with any ingested lactose and sucrose, is hydrolyzed by the appropriate disaccharidase (*maltase*, *lactase*, or *sucrase*) from the intestinal mucosa to glucose, galactose, and fructose.

These monosaccharides are absorbed across the wall of the duodenum and ileum by an active, energy-requiring, carrier mediated transfer process. The rate of absorption for glucose and galactose is several times greater than for similar molecules absorbed by passive diffusion (eg, xylose). Some conversion of fructose to glucose may occur during the process of absorption, and the inter conversion can be visualized in terms of the enediol form common to both. Fructose is absorbed more slowly than glucose and galactose by a carrier-mediated process different from glucose and galactose transport mechanisms. The monosaccharides are then transported by the portal vein to the liver.



Regulation of Blood Glucose Concentration

The concentration of glucose in the blood is regulated by the complex interplay of multiple pathways, modulated by several hormones. *Glycogenesis* is the conversion of glucose to glycogen. The reverse process—namely, the breakdown of glycogen to glucose and other intermediate products—is termed *glycogenolysis.* The formation of glucose from non-carbohydrate sources, such as amino acids, glycerol, or lactate, is termed *gluconeogenesis.* The conversion of glucose or other hexoses into lactate or pyruvate is called *glycolysis.* Further oxidation to carbon dioxide and water occurs through the Krebs (citric acid) cycle and the mitochondrial electron transport chain coupled to oxidative phosphorylation, generating energy in the form of adenosine triphosphate (ATP). Oxidation of glucose to carbon dioxide and water also occurs through the hexose monophosphate shunt pathway, which produces

NADPH. Discussion of the hormones that regulate blood glucose is provided in.

Categories of Increased Risk for Diabetes

People who have blood glucose concentrations above normal, but less than those required for a diagnosis of diabetes mellitus, have been recognized for many years. In 1979, this intermediate category was termed *impaired glucose tolerance* (IGT). It was defined as a 2-hour post load plasma glucose following an OGTT of 140 to 199 mg/dL (7.8–11.1 mmol/L). An OGTT is required to assign a patient to this class. To avoid an OGTT, the category of impaired fasting glucose (IFG) was added in 1997 by the ADA1 and by the WHO in 1999. IFG is diagnosed by a fasting glucose value between those of normal and diabetic individuals—namely, between 100 and 125 mg/dL (5.6 and 6.9 mmol/L). (Note that the WHO and a number of other diabetes organizations define the cutoff for IFG at 110 mg/mL (6.1 mmol/L). In 2009, hemoglobin A1c (HbA1c) was added as a criterion to diagnose diabetes. People with HbA1c values below the cutoff for diabetes—that is, 6.5% (48 mmol/mol)—but above the reference interval are at high risk of developing diabetes. For example, the incidence of diabetes in people with HbA1c between 6.0% and less than 6.5% (42 and 48 mmol/mol) is more than 10 times that of people with lower concentrations. Prospective studies reveal a 5-year cumulative incidence of diabetes ranging from 12% to 25% (three- to eightfold higher than the general population) for people with HbA1c of 5.5% to 6.0% (37–42 mmol/mol). Individuals with IFG and/or IGT and/or intermediate HbA1c (5.7% to 6.4%; 39–46 mmol/mol) have been referred to as having “prediabetes” because they are at high risk for progressing to diabetes. Moreover, they are at increased risk for the development of cardiovascular disease.

HORMONES THAT REGULATE BLOOD GLUCOSE CONCENTRATION

During a brief fast, a precipitous decline in the concentration of blood glucose is prevented by breakdown of glycogenstored in the liver and synthesis of glucose in the liver. Some glucose is derived from gluconeogenesis in the kidneys. These organs contain glucose-6-phosphatase, which is necessary to convert glucose 6-phosphate (derived from gluconeogenesis or glycogenolysis) to glucose. Skeletal muscle lacks this enzyme; muscle glycogen therefore cannot contribute directly to blood glucose. With more prolonged fasting (>42 hours), gluconeogenesis accounts for essentially all glucose production. In contrast, after a meal, the absorbed glucose is converted to glycogen (for storage in the liver and skeletal muscle) or fat (for storage in adipose tissue). Despite large fluctuations in the supply and demand of carbohydrates, the concentration of glucose in the blood is normally maintained within a fairly narrow range by hormones that modulate the Movement of glucose into and out of the circulation. These include insulin, which decreases blood glucose, and the counter regulatory hormones (glucagon, epinephrine, cortisol, and growth hormone), which increase blood glucose concentrations.

Normal glucose disposal depends on:

(1) The ability of the pancreas to secrete insulin.

(2) The ability of insulin to promote uptake of glucose into peripheral tissue.

(3) The ability of insulin to suppress hepatic glucose production.

The major insulin target organs are liver, skeletal muscle, and adipose tissue. These organs exhibit some differences in their responses to insulin. For example, the hormone stimulates glucose uptake through a specific glucose transporter—GLUT4—into muscle and fat cells but not into liver cells.

Diabetes Mellitus

Diabetes mellitus is a common disorder, in which patients develop hyperglycemia due to inadequate insulin secretion, defective insulin action, or both. The two major forms of diabetes are type 1 and type 2. The estimated global prevalence of diabetes is approximately 380 million. Many patients with diabetes develop severe debilitating complications, including blindness, renal failure, myocardial infarction peripheral vascular disease, and stroke.

Diabetes was initially diagnosed by the OGTT. Values greater than two standard deviations above the mean of the value found in a selected population of healthy volunteers without a family history of diabetes mellitus were accepted as diagnostic. This criterion led to the identification of large numbers of asymptomatic people with abnormally high 1- to 2-hour post load glucose values but normal fasting blood glucose. They were presumed to have early or mild diabetes mellitus. In 1975, it was estimated that more than half the population older than 60 years was abnormal. Follow-up of these individuals indicated that most of them with lesser degrees of glucose intolerance did not manifest definite evidence of diabetes mellitus in the next 10 years, and a large percentage returned to normal glucose tolerance. Most populations have plasma glucose values that exhibit a uni-modal, log-normal distribution (a distribution curve that is skewed to the high end but becomes bell shaped on a logarithmic axis). Ethnic groups with a high prevalence of diabetes,

such as the Pima Indians and Nauruans, exhibit bimodal blood glucose distributions. Optimal distinction between normal and diabetic individuals in these groups occurs at a fasting glucose around 140 mg/dL (7.8 mmol/L) and glucose concentrations greater than 200 mg/dL (11.1 mmol/L) hours after an oral glucose load. Furthermore, the specific microvascular complications of diabetes were believed to be rare in patients with fasting or 2-hour postprandial plasma glucose concentrations less than 140 or 200 mg/dL (7.8 or 11.1 mmol/L), respectively. These observations formed the basis for the criteria proposed in 1979 by a workgroup of the National Diabetes Data Group and later endorsed by the World Health Organization (WHO) Committee on Diabetes. Lower diagnostic values are used currently. The 1979 classification scheme recognized two major forms of diabetes: type 1 (insulin-dependent) diabetes mellitus (IDDM) and type 2 (non-insulin-dependent) diabetes mellitus (NIDDM).The terms *juvenile-onset* and *adult-onset diabetes* were abolished. To base the classification on cause rather than on treatment, the American Diabetes Association (ADA) established a workgroup in 1995 to reexamine the classification and diagnosis of diabetes mellitus. The revised classification, published in 19971 eliminates the terms *insulin-dependent diabetes mellitus* and *non-insulin-dependent diabetes mellitus,* which now are termed *type 1* and *type 2 diabetes,* respectively. Furthermore, the categories of previous abnormality of glucose tolerance and potential abnormality of glucose tolerance have been eliminated.

DIAGNOSIS

For many years the diagnosis of diabetes mellitus was dependent solely on the demonstration of hyperglycemia. In 2009, an International Expert Committee recommended that diabetes be diagnosed by

measurement of hemoglobin A1c (HbA1c), which reflects long-term blood glucose concentrations (for additional information, see "Glycated Hemoglobin" section in this chapter). For type 1 diabetes, the diagnosis is usually easy because hyperglycemia appears abruptly, is severe, and is accompanied by serious metabolic derangements. Diagnosis of type 2 diabetes may be difficult because hyperglycemia often is not severe enough for the patient to notice symptoms of diabetes. Nevertheless, the risk of complications makes it important to identify people with the disease. The diagnostic criteria recommended in 1979 included the following:

• Classic symptoms of diabetes with unequivocal increase in plasma glucose.

• FPG greater than or equal to 140 mg/dL (7.8 mmol/L) on more than one occasion.

• A 2-hour and one other postload glucose concentration greater than or equal to 200 mg/dL (11.1 mmol/L) during an OGTT. These criteria were widely adopted but are imperfect. The OGTT is more sensitive for diagnosis than fasting glucose early in the course of type 2 diabetes, resulting in lack ofequivalence between fasting and 2-hour glucose values. Virtually all persons with an FPG concentration of 140 mg/ dL (≥ 7.8 mmol/L) or greater have 2-hour glucose of 200 mg/ dL (≥11.1 mmol/L) or greater in an OGTT. In contrast, in persons without previously identified diabetes, fasting glucose of 140 mg/dL (≥7.8 mmol/L) or greater is present in only 25% of those who have 2-hour glucose of 200 mg/ dL (≥11.1 mmol/L) or greater. To address these and other discrepancies, the diagnostic criteria were revised in 1997. The major modification was lowering the diagnostic threshold for fasting glucose from 140 to 126 mg/ dL (7.8 to 7.0 mmol/L) to better identify

individuals at risk of retinopathy and nephropathy. The lower cutoff was suggested to provide earlier diagnosis of diabetes, with consequent earlier therapeutic intervention.

SUMMARY

1. Diabetes mellitus is a common medical condition, and an understanding of its biochemistry aids its medical management. Type 1 diabetes mellitus is associated with insulin deficiency and may present with weight loss and urinary ketones in young individuals. There is a relationship with autoimmune disease. Treatment is with insulin. Conversely, type 2 diabetes mellitus is usually associated with insulin resistance, increased body weight and later age presentation. There may be a family history of diabetes mellitus. Treatment involves diet and biguanides, sulphonylureas, glitazones or incretins, although insulin may sometimes be needed.
2. Biochemical tests have a major role in the management of diabetes mellitus and in monitoring its complications, such as in the control of blood glucose, HbA1c, plasma lipids and urinary ACR.
3. Diabetes mellitus can present with various comas, including hypoglycaemia, diabetic ketoacidosis (type 1), HONK and lactic acidosis.
4. Hypoglycaemia can present with neurological impairment and coma. A useful classification is to divide hypoglycaemia into that with high plasma insulin and that with low insulin levels. The causes of hyperinsulinaemic hypoglycaemia include insulinomas and following insulin administration. The causes of hypoinsulinaemic hypoglycaemia include severe hepatic disease, adrenal insufficiency, pituitary failure and non-pancreatic tumours producing insulin-like substances.