CHAPTER
32

Diabetes Mellitus

Diabetes mellitus is a chronic health problem affecting more than 15.7 million people in the United States.[1] The disease affects people in all age groups and from all walks of life. It is more prevalent among African Americans (9.6%) and Hispanic Americans (10.9%) compared with whites (6.2%).[1] Diabetes is a significant risk factor in coronary heart disease and stroke, and it is the leading cause of blindness and end-stage renal disease, as well as a major contributor to lower extremity amputations.

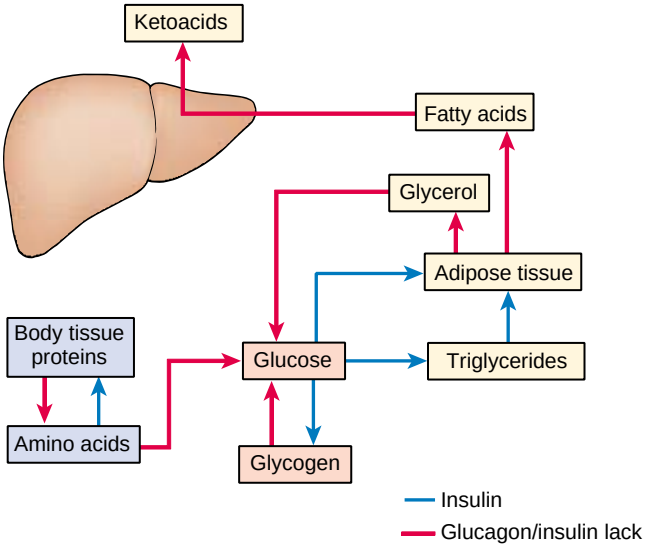
ENERGY METABOLISM

Diabetes is a disorder of energy metabolism resulting from an imbalance between insulin availability and insulin need. Although the respiratory and circulatory systems combine efforts to furnish the body with the oxygen needed for metabolic purposes, it is the hormones from the endocrine pancreas (mainly insulin and glucagon) in concert with the liver, that control the availability and utilization of glucose, fat, and protein as a fuel for metabolic processes (Fig. 32-1).

Glucose, Fat, and Protein Metabolism

Glucose Metabolism

Glucose is a six-carbon molecule; it is an efficient fuel that, when metabolized in the presence of oxygen, breaks down to form carbon dioxide and water. Although many tissues and organ systems are able to use other forms of fuel, such as fatty acids and ketones, the brain and nervous system rely almost exclusively on glucose as a fuel source. Because the brain can neither synthesize nor store more than a few minutes' supply of glucose, normal cerebral function requires a continuous supply from the circulation. Severe and prolonged hypoglycemia



■ **FIGURE 32-1** ■ Effect of insulin on glucose, fat, and protein metabolism.

can cause brain death, and even moderate hypoglycemia can result in substantial brain dysfunction.

Body tissues obtain glucose from the blood. Blood glucose levels usually reflect the difference between the amount of glucose released into the circulation by the liver and the amount of glucose removed from the blood by body cells. Glucose is ingested in the diet and transported from the gastrointestinal tract, through the portal vein, to the liver before it gains access to the circulatory system. The liver regulates blood glucose through three processes: (1) glycogen synthesis (glycogenesis), (2) glycogen breakdown (glycogenolysis), and (3) synthesis of glucose from noncarbohydrate sources (gluconeogenesis). When blood glucose levels rise, it is removed from the blood and converted to glycogen, the main short-term storage form of glucose. When blood glucose levels fall, the liver glycogen stores are broken down and released into the circulation. Although skeletal muscle also participates in glycogen storage, it lacks the enzyme glucose-6-phosphatase that allows glucose to be broken down sufficiently to pass through the cell membrane and enter the circulation, limiting its usefulness to the muscle cell.

In addition to mobilizing its glycogen stores, the liver synthesizes glucose from noncarbohydrate sources such as amino acids, lactic acid, and the glycerol part of triglycerides. This glucose may be stored as glycogen or it may be released directly into the circulation.

Fat Metabolism

Fat is the most efficient form of fuel storage. It provides 9 kcal/g of stored energy, compared with the 4 kcal/g provided by carbohydrates and proteins. About 40% of the calories in the normal American diet are obtained from fats, which is about equal to the amount obtained from carbohydrates. Therefore, the use of fats by the body for energy is as important as the use of carbohydrates. In addition, many of the carbohydrates consumed in the diet are converted to triglycerides for storage in adipose tissue.

A triglyceride contains three fatty acids linked by a glycerol molecule. The mobilization of fatty acids for use as an energy source is facilitated by the action of enzymes (lipases) that break triglycerides into a glycerol molecule and three fatty acids. The glycerol molecule can enter the glycolytic pathway and be used along with glucose to produce energy, or it can be used to produce glucose. The fatty acids are transported to tissues where they are utilized for energy. Almost all cells, with the exception of brain tissue and red blood cells, can use fatty acids interchangeably with glucose for energy. Although many cells use fatty acids as a fuel source, fatty acids cannot be converted to glucose that can be used by the brain for energy.

A large share of the initial degradation of fatty acids occurs in the liver, especially when excessive amounts of fatty acids are being used for energy. The liver uses only a small amount of the fatty acids for its own energy needs; it converts the rest into ketones and releases them into the blood. In situations that favor fat breakdown, such as diabetes mellitus and fasting, large amounts of ketones are released into the bloodstream. Because ketones are organic acids, they cause ketoacidosis when they are present in excessive amounts.

Protein Metabolism

Approximately three fourths of body solids are proteins. Proteins are essential for the formation of all body structures, including genes, enzymes, contractile structures in muscle, matrix of bone, and hemoglobin of red blood cells.

Amino acids are the building blocks of proteins. Significant quantities of amino acids are present in body proteins. Unlike glucose and fatty acids, there is only a limited facility for the storage of excess amino acids in the body. Most of the stored amino acids are contained in body proteins. Amino acids in excess of those needed for protein synthesis are converted to fatty acids, ketones, or glucose and are stored or used as metabolic fuel. Because fatty acids cannot be converted to glucose, the body must break down proteins and use the amino acids as a major substrate for gluconeogenesis during periods when metabolic needs exceed food intake.

Hormonal Control of Blood Glucose

The hormonal control of blood glucose resides largely with the endocrine pancreas. The pancreas is made up of two major tissue types: the acini and the islets of Langerhans (Fig. 32-2). The

acini secrete digestive juices into the duodenum, and the islets of Langerhans secrete glucose-regulating hormones into the blood. Each islet is composed of beta cells that secrete insulin, alpha cells that secrete glucagon, and delta cells that secrete somatostatin. Insulin lowers the blood glucose concentration by facilitating the movement of glucose into body tissues. Glucagon maintains blood glucose by increasing the release of glucose from the liver into the blood. Somatostatin inhibits the release of insulin and glucagon. Somatostatin also decreases gastrointestinal activity after ingestion of food. By decreasing gastrointestinal activity, somatostatin is thought to extend the time during which food is absorbed into the blood, and by inhibiting insulin and glucagon, it is thought to extend the use of absorbed nutrients by the tissues.[2]

Insulin

Although several hormones are known to increase blood glucose levels, insulin is the only hormone known to have a direct effect in lowering blood glucose levels. The actions of insulin are threefold; it (1) promotes glucose uptake by target cells and provides for glucose storage as glycogen, (2) prevents fat and glycogen breakdown and inhibits gluconeogenesis, and (3) increases protein synthesis (Table 32-1). Insulin acts to promote fat storage by increasing the transport of glucose into fat cells. It also facilitates triglyceride synthesis from glucose in fat cells and inhibits the intracellular breakdown of stored triglycerides. Insulin also inhibits protein breakdown and increases protein synthesis by increasing the active transport of amino acids into body cells. Insulin inhibits gluconeogenesis, or the building of glucose from new sources, mainly amino acids. When sufficient glucose and insulin are present, protein breakdown is minimal because the body is able to use glucose and fatty acids as a fuel source. In children and adolescents, insulin is needed for normal growth and development.

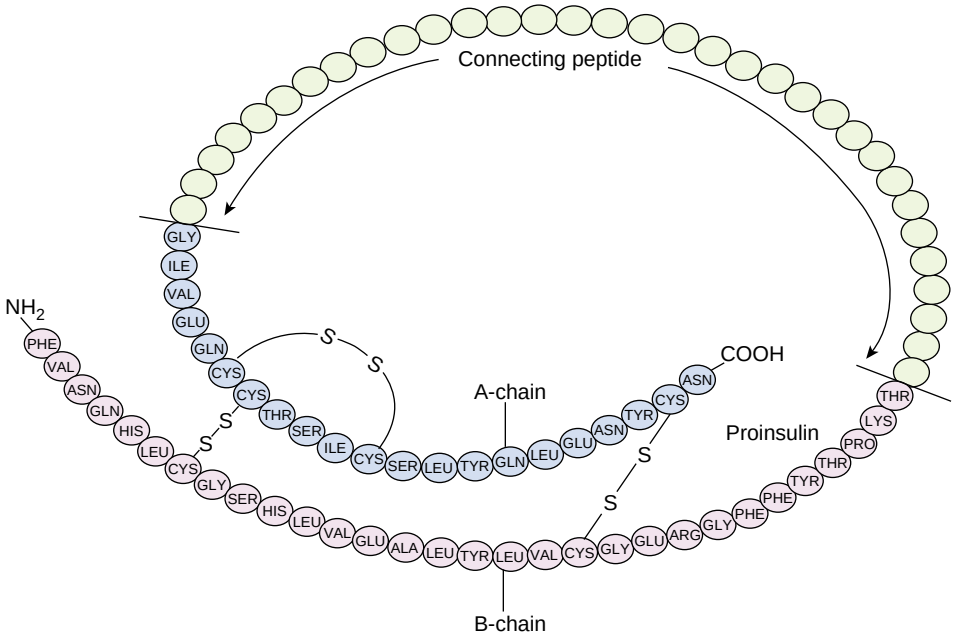
Insulin Synthesis and Release. Insulin is produced by the pancreatic beta cells in the islets of Langerhans. The active form of the hormone is composed of two polypeptide chains—an A chain and a B chain (Fig. 32-3). Active insulin is formed in the beta cells from a larger molecule called *proinsulin*. In converting proinsulin to insulin, enzymes in the beta cell cleave proinsulin at specific sites to form two separate substances: active insulin and a biologically inactive connecting peptide (C-peptide) chain that joined the A and B chains before they were separated. Active insulin and the inactive C-peptide chain are packaged into secretory granules and released simultaneously from the beta cell. The C-peptide chains can be measured clinically, and this measurement can be used to study beta cell activity. For example, injected (exogenous) insulin in a person with type 2 diabetes would provide few or no C-peptide chains, whereas insulin (endogenous) secreted by the beta cells would be accompanied by the secretion of C-peptide chains.

The release of insulin from the pancreatic beta cells is regulated by blood glucose levels, increasing as blood glucose levels rise and decreasing when blood glucose levels decline. Secretion of insulin occurs in an oscillatory or pulsatile fashion. After exposure to glucose, a first-phase release of stored preformed insulin occurs, followed by a second-phase release of newly synthesized insulin (Fig. 32-4). Serum insulin levels begin to rise within minutes after a meal, reach a peak in approximately 3 to 5 minutes, and then return to baseline levels within 2 to 3 hours.

Insulin secreted by the beta cells enters the portal circulation and travels directly to the liver, where approximately 50% is used or degraded. Insulin, which is rapidly bound to peripheral tissues or destroyed by the liver or kidneys, has a half-life of approximately 15 minutes once it is released into the general circulation.

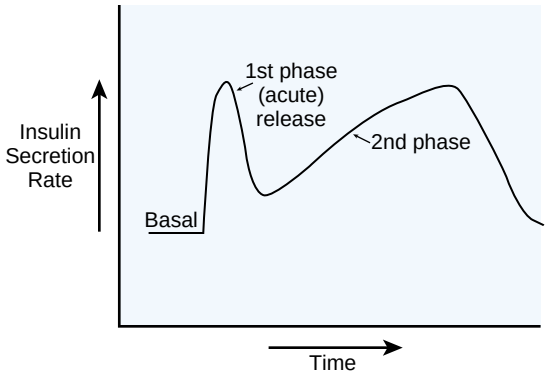
TABLE 32-1 Actions of Insulin and Glucagon on Glucose, Fat, and Protein Metabolism

	Insulin	Glucagon
Glucose		
Glucose transport	Increases glucose transport into skeletal muscle and adipose tissue	
Glycogen synthesis	Increases glycogen synthesis	Promotes glycogen breakdown
Gluconeogenesis	Decreases gluconeogenesis	Increases gluconeogenesis
Fats		
Triglyceride synthesis	Increases triglyceride synthesis	
Triglyceride transport into adipose tissue	Increases fatty acid transport into adipose cells	Enhances lipolysis in adipose tissue, liberating fatty acids and glycerol for use in gluconeogenesis
Activation of adipose cell lipase	Inhibits adipose cell lipase Activates lipoprotein lipase in capillary walls	Activates adipose cell lipase
Proteins		
Amino acid transport	Increases active transport of amino acids into cells	Increases transport of amino acids into hepatic cells
Protein synthesis	Increases protein synthesis by increasing transcription of messenger RNA and accelerating protein synthesis by ribosomal RNA	Increases breakdown of proteins into amino acids for use in gluconeogenesis
Protein breakdown	Decreases protein breakdown by enhancing the use of glucose and fatty acids as fuel	Increases conversion of amino acids into glucose precursors



■ **FIGURE 32-3** ■ Structure of proinsulin. With removal of the connecting peptide (C-peptide), proinsulin is converted to insulin.

Insulin Receptors and Target Cell Effects. To initiate its effects on target tissues, insulin binds to and activates a membrane receptor. It is the activated receptor that is responsible for the cellular effects of insulin.[2] The insulin receptor is a combination of four subunits—a large α subunit that extends outside the cell membrane and is involved in insulin binding and a smaller β subunit that is predominantly inside the cell membrane and contains a kinase enzyme that becomes activated during insulin binding (Fig. 32-5). Activation of the kinase enzyme results in phosphorylation of the β subunit, which in turn activates some enzymes and inactivates others, thereby directing the desired intracellular effect of insulin on glucose, fat, and protein metabolism.



■ **FIGURE 32-4** ■ Biphasic insulin response to a constant glucose stimulus. The peak of the first phase in humans is 3 to 5 minutes; the second phase begins at 2 minutes and continues to increase slowly for at least 60 minutes or until the stimulus stops. (From Ward W.K., Beard J.C., Halter J.B., Pfeifer M.A., Porte D. Jr. [1984]. Pathology of insulin secretion in non-insulin-dependent diabetes mellitus. *Diabetes Care* 7, 491–502. Used with permission.)

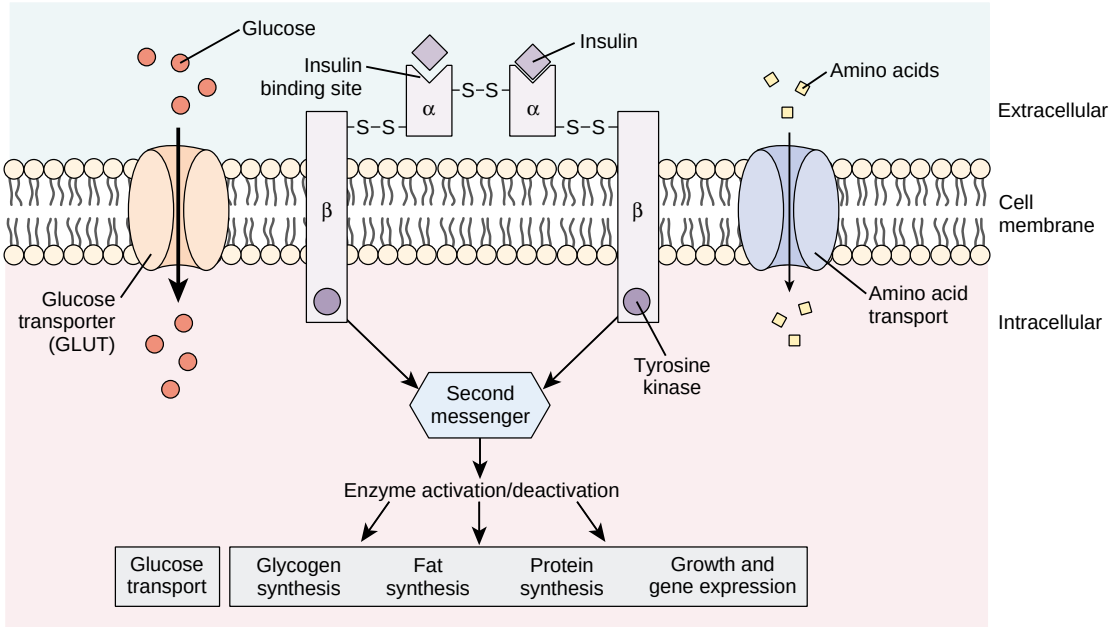
Glucose Transporters. Because cell membranes are impermeable to glucose, they require a special carrier, called a *glucose transporter*, to move glucose from the blood into the cell. Within seconds after insulin binds to its membrane receptor, the membranes of about 80% of body tissues increase their uptake of glucose by means of special glucose transporters. This is particularly true of skeletal muscle and adipose tissues.

Considerable research has revealed a family of glucose transporters termed *GLUT-1*, *GLUT-2*, and so forth.[3] GLUT-4 is the insulin-dependent glucose transporter for skeletal muscle and adipose tissue (Fig. 32-6). It is sequestered inside the membrane of these cells and thus is unable to function as a glucose transporter until a signal from insulin causes it to move from its inactive site into the cell membrane, where it facilitates glucose entry. GLUT-2 is the major transporter of glucose into beta cells and liver cells. It has a low affinity for glucose and acts as a transporter only when plasma glucose levels are relatively high, such as after a meal. GLUT-1 is present in all tissues. It does not require the actions of insulin and is important in transport of glucose into the nervous system.

Glucagon

Glucagon, a polypeptide molecule produced by the alpha cells of the islets of Langerhans, maintains blood glucose between meals and during periods of fasting. Like insulin, glucagon travels through the portal vein to the liver, where it exerts its main action. Unlike insulin, glucagon produces an increase in blood glucose (see Table 32-1). The most dramatic effect of glucagon is its ability to initiate *glycogenolysis* or the breakdown of liver glycogen as a means of raising blood glucose, usually within a matter of minutes. Because liver glycogen stores are limited, gluconeogenesis is important in maintaining blood glucose levels over time. Glucagon also increases the transport of amino acids into the liver and stimulates their conversion into glucose.

As with insulin, glucagon synthesis and secretion is regulated by blood glucose. A decrease in blood glucose concentration to



■ **FIGURE 32-5** ■ Insulin receptor. Insulin binds to the α subunits of the insulin receptor, which increases glucose transport and causes autophosphorylation of the β subunit of the receptor, which induces tyrosine kinase activity. Tyrosine phosphorylation, in turn, activates a cascade of intracellular signaling proteins that mediate the effects of glucose on insulin, fat, and protein metabolism.

■ **FIGURE 32-6** ■ Insulin-dependent glucose transporter (Glut-4). (1) binding of insulin to insulin receptor on the surface of the cell membrane, (2) generation of intracellular signal, (3) insertion of Glut-4 receptor from its inactive site into the cell membrane, and (4) transport of glucose across the cell membrane.

a hypoglycemic level produces an immediate increase in glucagon secretion, and an increase in blood glucose to hyperglycemic levels produces a decrease in glucagon secretion. High concentrations of amino acids, as occur after a protein meal, also can stimulate glucagon secretion. In this way, glucagon increases the conversion of amino acids to glucose as a means of maintaining the body's glucose levels. Glucagon levels also increase during strenuous exercise as a means of preventing a decrease in blood glucose.

Other Hormones That Affect Blood Glucose

Other hormones that can affect blood glucose include the catecholamines, growth hormones, and the glucocorticoids. These hormones are sometimes called counter-regulatory hormones because they counteract the storage functions of insulin in regulating blood glucose levels during periods of fasting, exercise, and other situations that either limit glucose intake or deplete glucose stores.

Catecholamines. The catecholamines (epinephrine and norepinephrine) help to maintain blood glucose levels during periods of stress. Epinephrine inhibits insulin release and promotes glycogenolysis by stimulating the conversion of muscle and liver glycogen to glucose. Muscle glycogen cannot be released into the blood; nevertheless, the mobilization of these stores for muscle use conserves blood glucose for use by other tissues such as the brain and the nervous system. During periods of exercise and other types of stress, epinephrine inhibits insulin release from the beta cells and thereby decreases the movement of glucose into muscle cells. The catecholamines also increase lipase activity and thereby increase mobilization of fatty acids, a process that conserves glucose. The blood glucose-elevating effect of epinephrine is an important home-

ostatic mechanism during periods of hypoglycemia in insulin-treated diabetics.

Growth Hormone. Growth hormone has many metabolic effects. It increases protein synthesis in all cells of the body, mobilizes fatty acids from adipose tissue, and antagonizes the effects of insulin. Growth hormone decreases cellular uptake and use of glucose, thereby increasing the level of blood glucose. The increased blood glucose level stimulates further insulin secretion by the beta cells. The secretion of growth hormone normally is inhibited by insulin and increased levels of blood glucose. During periods of fasting, when both blood glucose levels and insulin secretion fall, growth hormone levels increase. Exercise, such as running and cycling, and various stresses, including anesthesia, fever, and trauma, increase growth hormone levels.

Chronic hypersecretion of growth hormone, as occurs in a condition called acromegaly (see Chapter 31), can lead to glucose intolerance and the development of diabetes mellitus. In children who already have diabetes, moderate elevations in growth hormone levels that occur during periods of growth can produce the entire spectrum of metabolic abnormalities associated with poor regulation, despite optimized insulin treatment.

Glucocorticoid Hormones. The glucocorticoid hormones, which are synthesized in the adrenal cortex along with other corticosteroid hormones, are critical to survival during periods of fasting and starvation. They stimulate gluconeogenesis by the liver, sometimes producing a 6- to 10-fold increase in hepatic glucose production. These hormones also moderately decrease tissue use of glucose. In predisposed persons, the prolonged elevation of glucocorticoid hormones can lead to hyperglycemia and the development of diabetes mellitus. In people with diabetes, even transient increases in cortisol can complicate control.

There are several steroid hormones with glucocorticoid activity; the most important of these is cortisol, which accounts for approximately 95% of all glucocorticoid activity (see Chapter 31). Cortisol levels increase during periods of stress, such as that produced by infection, pain, trauma, surgery, prolonged and strenuous exercise, and acute anxiety. Hypoglycemia is a potent stimulus for cortisol secretion.

In summary, hormones from the endocrine pancreas (mainly insulin and glucagon) in concert with the liver control the availability and utilization of glucose, fat, and protein as fuel sources for the metabolic needs of the body. The liver functions as an important glucose buffer system: it stores glucose when blood glucose levels rise, and it releases glucose when blood levels fall. Both insulin and glucagon function as important feedback systems for maintaining blood glucose levels. When blood glucose levels rise, insulin (which is secreted by the beta cells in the endocrine pancreas) increases the transport of glucose into body cells. Insulin also decreases hepatic glucose production and release, and it decreases lipolysis and the use of fats as a fuel source. When blood glucose levels fall, glucagon (which is released by the alpha cells in the endocrine pancreas) stimulates the liver to release glucose from its glycogen stores (glycogenolysis) and synthesize glucose from noncarbohydrate sources (gluconeogenesis).

Other hormones, including epinephrine, growth hormone, and the glucocorticoids, help to maintain blood glucose concentrations. Epinephrine inhibits insulin release and promotes glycogenolysis by stimulating the conversion of muscle and liver glycogen to glucose. Growth hormone antagonizes the effects of insulin, thereby decreasing cellular uptake and the use of glucose. It also mobilizes fatty acids from adipose tissue and increases protein synthesis. The glucocorticoid hormones stimulate the production and release of glucose by the liver.

DIABETES MELLITUS

The term *diabetes* is derived from a Greek word meaning "going through" and *mellitus* from the Latin word for "honey" or "sweet." Reports of the disorder can be traced to the first century AD, when Aretaeus the Cappadocian described the disorder as a chronic affection characterized by intense thirst and voluminous, honey-sweet urine: "the melting down of flesh into urine." It was the discovery of insulin by Banting and Best in 1922 that transformed the once-fatal disease into a manageable chronic health problem.[4]

Diabetes is a disorder of carbohydrate, protein, and fat metabolism resulting from an imbalance between insulin availability and insulin need. It can represent an absolute insulin deficiency, impaired release of insulin by the pancreatic beta cells, inadequate or defective insulin receptors, or the production of inactive insulin or insulin that is destroyed before it can carry out its action. A person with uncontrolled diabetes is unable to transport glucose into fat and muscle cells; as a result, the body cells are starved, and the breakdown of fat and protein is increased.

Classification and Etiology

Although diabetes mellitus clearly is a disorder of insulin availability, it probably is not a single disease. A revised system for the classification of diabetes was developed in 1997 by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus.[5] The intent of the revised system, which replaces the 1979 classification system, was to move away from a system that focused on the type of pharmacologic treatment used in management of diabetes to one based on disease etiology. The revised system continues to include type 1 and type 2 diabetes, but uses Arabic, rather than Roman, numerals and eliminates the use of "insulin-dependent" and "non–insulin-dependent" diabetes mellitus (Table 32-2). Type 1 diabetes is due to pancreatic beta cell destruction predominantly by an autoimmune process. Type 2 diabetes is the more prevalent type and results from insulin resistance. Included in the classification system are the categories of gestational diabetes mellitus (GDM; *i.e.*, diabetes that develops during pregnancy) and other specific types of diabetes, many of which occur secondary to other conditions (*e.g.*, Cushing's syndrome, pancreatitis, acromegaly).

The revised classification system also includes a system for diagnosing diabetes according to stages of glucose intolerance[5] (Table 32-3). The revised criteria have retained the former

TABLE 32-2 Etiologic Classification of Diabetes Mellitus

Type	Subtypes	Etiology of Glucose Intolerance
I. Type 1*	*(Beta cell destruction usually leading to absolute insulin deficiency)*	
	A. Immune-mediated	Autoimmune destruction of beta cells
	B. Idiopathic	Unknown
II. Type 2*	*(May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)*	
III. Other Specific Types	A. Genetic defects of beta cell function, *e.g.,* chromosome 7, glucokinase	Regulates insulin secretion due to defect in glucokinase generation
	B. Genetic defects in insulin action, *e.g.,* leprechaunism, Rabson-Mendenhall syndrome	Pediatric syndromes that have mutations in insulin receptors
	C. Diseases of the exocrine pancreas, *e.g.,* pancreatitis, neoplasms, cystic fibrosis	Loss or destruction of insulin-producing beta cells
	D. Endocrine disorders, *e.g.,* acromegaly, Cushing's syndrome	Diabetogenic effects of excess hormone levels
	E. Drug or chemical-induced, *e.g.,* Vacor, glucocorticoids, thiazide diuretics, α-Interferon	Toxic destruction of beta cells Insulin resistance Impaired insulin secretion Production of islet cell antibodies
	F. Infections, *e.g.,* congenital rubella, cytomegalovirus	Beta cell injury followed by autoimmune response
	G. Uncommon forms of immune-mediated diabetes, *e.g.,* "stiff man syndrome"	Autoimmune disorder of central nervous system with immune-mediated beta cell destruction
	H. Other genetic syndromes sometimes associated with diabetes, *e.g.,* Down syndrome, Klinefelter's syndrome, Turner's syndrome	Disorders of glucose tolerance related to defects associated with chromosomal abnormalities
IV. Gestational diabetes mellitus (GDM)	*(Any degree of glucose intolerance with onset or first recognition during pregnancy)*	Combination of insulin resistance and impaired insulin secretion

*Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient.

(Adapted from The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. [1997]. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care 20*, 1183–1197)

category of *impaired glucose tolerance* (IGT) and have added a new category of *impaired fasting blood glucose* (IFG). The categories of IFG and IGT refer to metabolic stages intermediate between normal glucose homeostasis and diabetes. A fasting blood glucose of 110 mg/dL or less or a 2-hour oral glucose tolerance test result of less than 140 mg/dL is considered normal. IFG is defined as a fasting blood glucose of 110 mg/dL or greater but less than 126 mg/dL. IGT reflects abnormal blood glucose measurements (≥140 mg/dL but <200 mg/dL) 2 hours after an oral glucose load.[5] Each year, approximately 5% of people with IFG and IGT experience progression to diabetes. IFG and IGT are associated with increased risk of atherosclerotic heart disease. Calorie restriction and weight reduction are important in overweight people with IFG and IGT.[6]

TABLE 32-3 National Diabetes Data Group for Interpretation of Fasting Plasma Glucose and Oral Glucose Tolerance With Use of Venous Plasma or Serum Using a 75-g Carbohydrate Load

Test	Normoglycemic	IFG	IGT	Diabetes Mellitus
Fasting plasma glucose (mg/dL)	<110	≥110–<126		≥126
Two-hour postload glucose (mg/dL)*	<140		≥140–<200	≥200
Other				Symptoms of diabetes mellitus and random plasma glucose ≥200

IFG, impaired fasting blood glucose; IGT, impaired glucose tolerance.

A diagnosis of diabetes mellitus must be confirmed on a subsequent day by any one of three methods included in the chart. In clinical settings, the fasting plasma glucose test is greatly preferred because of ease of administration, convenience, acceptability to patients, and lower cost. Fasting is defined as no caloric intake for at least 8 hours.

*This test requires the use of a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water.

KEY CONCEPTS

DIABETES MELLITUS

- Diabetes mellitus is a disorder of carbohydrate, fat, and protein metabolism brought about by impaired beta cell synthesis or release of insulin, or the inability of tissues to use glucose.
- Type 1 diabetes results from loss of beta cell function and an absolute insulin deficiency.
- Type 2 diabetes results from impaired ability of the tissues to use insulin accompanied by a relative lack of insulin or impaired release of insulin in relation to blood glucose levels.

Type 1 Diabetes Mellitus

Type 1 diabetes is caused by beta cell destruction and insulin deficiency. It is immune-mediated (type 1A) in more than 90% of cases and idiopathic (type 1B) in less than 10% of cases. Type 1 diabetes, formerly called *juvenile diabetes*, occurs more commonly in young persons but can occur at any age. The rate of beta cell destruction is quite variable, being rapid in some individuals and slow in others. The rapidly progressive form commonly is observed in children but also may occur in adults. The slowly progressive form usually occurs in adults and is sometimes referred to as *latent autoimmune diabetes in adults*. In the United States and Europe, approximately 10% of people with diabetes mellitus have type 1 diabetes.

Type 1 diabetes is a catabolic disorder in which circulating insulin is virtually absent, glucagon levels are elevated, and pancreatic beta cells fail to respond to all insulin-producing stimuli. One of the actions of insulin is the inhibition of *lipolysis* (*i.e.*, fat breakdown) and release of free fatty acids (FFA) from fat cells. In the absence of insulin, ketosis develops when these fatty acids are released from fat cells and converted to ketoacids in the liver. Because of the loss of beta function and complete lack of insulin, all people with type 1A diabetes require exogenous insulin replacement to reverse the catabolic state, control blood glucose levels, and prevent ketosis.

Type 1 diabetes is thought to result from genetic predisposition (*i.e.*, diabetogenic genes), a hypothetical triggering event that involves an environmental agent that incites an immune response and the production of autoantibodies that destroy beta cells. These autoantibodies may exist for years before the onset of hyperglycemia. Certain inherited human leukocyte antigens (HLA) are strongly associated with the development of type 1 diabetes. About 95% of persons with the disease have either HLA-DR3 or HLA-DR4 (see Chapter 8). The fact that type 1 diabetes is thought to result from an interaction between genetic and environmental factors has led to research into methods directed at prevention and early control of the disease. These methods include the identification of genetically susceptible persons and early intervention in persons with newly diagnosed type 1 diabetes. After the diagnosis of type 1 diabetes, there often is a short period of beta cell regeneration, during which symptoms of diabetes disappear and insulin injections are not needed. This is sometimes called the *honeymoon period*. Immune interventions designed to interrupt the destruction of beta cells before development of type 1 diabetes are being investigated in the Diabetes Prevention Trial, which is trying to find a way to prevent complete and irreversible beta cell failure.

The term *idiopathic form of type 1 diabetes* is used to describe those cases of beta cell destruction in which no evidence of autoimmunity is present. Only a small number of people with type 1 diabetes fall into this category; most are of African or Asian descent. Type 1B diabetes is strongly inherited. People with the disorder have episodic ketoacidosis caused by varying degrees of insulin deficiency with periods of absolute insulin deficiency that may come and go.

Type 2 Diabetes Mellitus

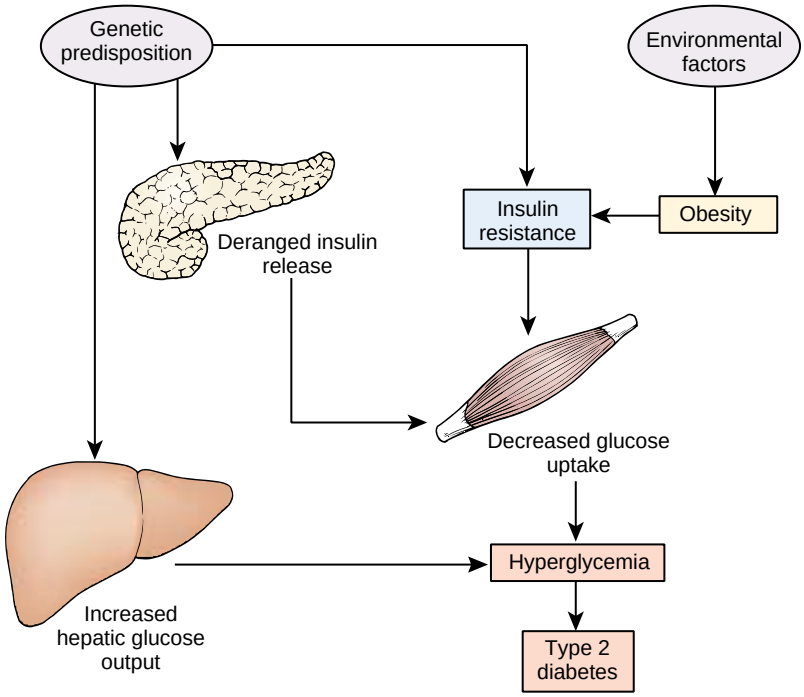
Type 2 diabetes mellitus describes a condition of fasting hyperglycemia that occurs despite the availability of insulin. In contrast to type 1 diabetes, type 2 diabetes is not associated with HLA markers or autoantibodies. Most people with type 2 diabetes are older and overweight. The metabolic abnormalities that contribute to hyperglycemia in people with type 2 diabetes include (1) impaired insulin secretion, (2) peripheral insulin resistance, and (3) increased hepatic glucose production (Fig. 32-7). Insulin resistance initially stimulates insulin secretion from the beta cells in the pancreas to overcome the increased demand to maintain a normoglycemic state. In time, the insulin response by the beta cells declines because of exhaustion. This results in elevated postprandial blood glucose levels. During the evolutionary phase, an individual with type 2 diabetes may not produce sufficient amounts of insulin levels because of beta cell failure. Because people with type 2 diabetes do not have an absolute insulin deficiency, they are less prone to ketoacidosis than are people with type 1 diabetes.

There also is evidence to suggest that insulin resistance not only contributes to the hyperglycemia in persons with type 2 diabetes, but also may play a role in other metabolic abnormalities. These include high levels of plasma triglycerides, low levels of high-density lipoproteins, hypertension, abnormal fibrinolysis, and coronary heart disease. This constellation of abnormalities often is referred to as the *insulin resistance syndrome, syndrome X*, or *the metabolic syndrome*.[7]

Approximately 80% of persons with type 2 diabetes are overweight.[8] The presence of obesity and the type of obesity are important considerations in the development of type 2 diabetes. It has been found that people with upper body obesity are at greater risk for developing type 2 diabetes than are persons with lower body obesity (see Chapter 29). Obese people have increased resistance to the action of insulin and impaired suppression of glucose production by the liver, resulting in both hyperglycemia and hyperinsulinemia. The increased insulin resistance has been attributed to increased visceral (intra-abdominal) fat detected on computed tomography scan.[9] In addition to increased insulin resistance, insulin release from beta cells in response to glucose is impaired. Over time, insulin resistance may improve with weight loss, to the extent that many people with type 2 diabetes can manage the condition with a weight-reduction program and exercise.

Other Specific Types

The category of other specific types of diabetes, formerly known as *secondary diabetes*, describes diabetes that is associated with certain other conditions and syndromes. Such diabetes can



■ **FIGURE 32-7** ■ Pathogenesis of type 2 diabetes mellitus.

occur with pancreatic disease or the removal of pancreatic tissue and with endocrine diseases, such as acromegaly or Cushing's syndrome. Endocrine disorders that produce hyperglycemia do so by increasing the hepatic production of glucose or decreasing the cellular use of glucose. Several specific types of diabetes are associated with monogenetic defects in beta cell function. These specific types of diabetes, which resemble type 2 diabetes but occur at an earlier age (usually before 25 years of age), were formerly referred to as *maturity-onset diabetes of the young* (MODY).[10]

Environmental agents that have been associated with altered pancreatic beta cell function include viruses (*e.g.*, mumps, congenital rubella, coxsackievirus) and chemical toxins. Among the suspected chemical toxins are the nitrosamines, which sometimes are found in smoked and cured meats. The nitrosamines are related to streptozocin, which is used to induce diabetes in experimental animals, and to the rat poison Vacor, which can produce diabetes when ingested by humans.

Several diuretics—thiazides and loop diuretics—elevate blood glucose. These diuretics increase potassium loss, which is thought to impair insulin release. Other drugs known to cause hyperglycemia are diazoxide, glucocorticoids, levodopa, oral contraceptives, sympathomimetics, phenothiazines, phenytoin, and total parenteral nutrition (*i.e.*, hyperalimentation). Drug-related increases in blood glucose usually are reversed after use of the drug has been discontinued.

Gestational Diabetes

Gestational diabetes mellitus refers to glucose intolerance that is detected first during pregnancy. It occurs to various degrees in 2% to 5% of pregnancies.[11] It most frequently affects women with a family history of diabetes; with glycosuria; with a history of stillbirth or spontaneous abortion, fetal anomalies in a previous pregnancy, or a previous large- or heavy-for-date infant; and those who are obese, of advanced maternal age, or have had five or more pregnancies.

Diagnosis and careful medical management are essential because women with GDM are at higher risk for complications of pregnancy, mortality, and fetal abnormalities.[12] Fetal abnormalities include macrosomia (*i.e.*, large body size), hypoglycemia, hypocalcemia, polycythemia, and hyperbilirubinemia. The American Diabetes Association (ADA) Clinical Practice Recommendations suggest that pregnant women who have not been identified as having glucose intolerance before the 24th week have a screening glucose tolerance test between the 24th and 28th week of pregnancy.[11] However, women who are younger than 25 years, were of normal body weight before pregnancy, have no family history of diabetes or poor obstetric outcome, and are not members of a high-risk ethnic/racial group (*e.g.*, Hispanic, Native American, Asian, African American) may not need to be screened.

Treatment of GDM includes close observation of mother and fetus because even mild hyperglycemia has been shown to be detrimental to the fetus. Maternal fasting and postprandial blood glucose levels should be measured regularly. Fetal surveillance depends on the degree of risk for the fetus. The frequency of growth measurements and determinations of fetal distress depends on available technology and gestational age. All women with GDM require nutritional guidance because nutrition is the cornerstone of therapy. The nutrition plan should provide the necessary nutrients for maternal and fetal health, result in normoglycemia and proper weight gain, and prevent ketosis.[12] If dietary management alone does not achieve a fasting blood glucose level no greater than 105 mg/dL or a 2-hour postprandial blood glucose no greater than 120 mg/dL, the Third International Workshop on GDM recommends therapy

with human insulin. Oral antidiabetic agents may be teratogenic and are not recommended in pregnancy. Self-monitoring of blood glucose levels is essential.

Women with GDM are at increased risk for the development of diabetes 5 to 10 years after delivery. Women in whom GDM is diagnosed should be followed up after delivery to detect diabetes early in its course. These women should be evaluated during their first postpartum visit with a 2-hour oral glucose tolerance test with a 75-g glucose load.

Manifestations of Diabetes

Diabetes mellitus may have a rapid or an insidious onset. In type 1 diabetes, signs and symptoms often arise suddenly. Type 2 diabetes usually develops more insidiously. Its presence may be detected during a routine medical examination or when a patient seeks medical care for other reasons.

The most commonly identified signs and symptoms of diabetes are referred to as the *three polys*—polyuria (*i.e.*, excessive urination), polydipsia (*i.e.*, excessive thirst), and polyphagia (*i.e.*, excessive hunger). These three symptoms are closely related to the hyperglycemia and glycosuria of diabetes. Glucose is a small, osmotically active molecule. When blood glucose levels are sufficiently elevated, the amount of glucose filtered by the glomeruli of the kidney exceeds the amount that can be reabsorbed by the renal tubules. This results in glycosuria accompanied by large losses of water in the urine. Thirst results from the intracellular dehydration that occurs as blood glucose levels rise and water is pulled out of body cells, including those in the thirst center. Cellular dehydration also causes dryness of the mouth. This early symptom may be easily overlooked in people with type 2 diabetes, particularly in those who have had a gradual increase in blood glucose levels. Polyphagia usually is not present in people with type 2 diabetes. In type 1 diabetes, it probably results from cellular starvation and the depletion of cellular stores of carbohydrates, fats, and proteins.

Weight loss despite normal or increased appetite is a common occurrence in people with uncontrolled type 1 diabetes. The cause of weight loss is twofold. First, loss of body fluids results from osmotic diuresis. Vomiting may exaggerate the fluid loss in ketoacidosis. Second, body tissue is lost because the lack of insulin forces the body to use its fat stores and cellular proteins as sources of energy. In terms of weight loss, there often is a marked difference between type 2 diabetes and type 1 diabetes. Weight loss is a common phenomenon in people with uncontrolled type 1 diabetes, whereas many people with uncomplicated type 2 diabetes have problems with obesity.

Other signs and symptoms of hyperglycemia include recurrent blurred vision, fatigue, paresthesias, and skin infections. In type 2 diabetes, these often are the symptoms that prompt a person to seek medical treatment. Blurred vision develops as the lens and retina are exposed to hyperosmotic effects of elevated blood glucose levels. Lowered plasma volume produces weakness and fatigue. Paresthesias reflect a temporary dysfunction of the peripheral sensory nerves. Chronic skin infections are common in people with type 2 diabetes. Hyperglycemia and glycosuria favor the growth of yeast organisms. Pruritus and vulvovaginitis resulting from candidal infections are common initial complaints in women with diabetes.

Diagnostic Methods

The diagnosis of diabetes mellitus in nonpregnant adults is based on fasting blood glucose levels, random blood glucose tests, or the results of a glucose challenge test (see Table 32-3). Testing for diabetes should be considered in all individuals 45 years of age and older. Testing should be considered at a younger age in people who are obese, have a first-degree relative with diabetes, are members of a high-risk group, women who have delivered an infant weighing more than 9 pounds or have received a diagnosis of GDM, have hypertension or hyperlipidemia, or have met the criteria for IGT or IFG on previous testing.[13]

Blood Tests

Blood glucose measurements are used in both the diagnosis and management of diabetes. Diagnostic tests include the fasting blood glucose, random blood glucose, the glucose tolerance test, and glycosylated hemoglobin. Laboratory and capillary, or "finger stick," glucose tests are used for glucose management in people with diagnosed diabetes.

The *fasting blood glucose* has been suggested as the preferred diagnostic test because of ease of administration, convenience, patient acceptability, and cost.[5] Glucose levels are measured after food has been withheld for 8 to 12 hours. If the fasting plasma glucose level is higher than 126 mg/dL on two occasions, diabetes is diagnosed (see Table 32-3). A random blood glucose is one that is done without regard to meals or time of day. A random blood glucose concentration that is unequivocally elevated (>200 mg/dL) in the presence of classic symptoms of diabetes such as polydipsia, polyphagia, polyuria, and blurred vision is diagnostic of diabetes mellitus at any age.

The *oral glucose tolerance test* is an important screening test for diabetes. The test measures the body's ability to store glucose by removing it from the blood. In people with normal glucose tolerance, blood glucose levels return to normal within 2 to 3 hours after ingestion of a glucose load, in which case it can be assumed that sufficient insulin is present to allow glucose to leave the blood and enter body cells. Because a person with diabetes lacks the ability to respond to an increase in blood glucose by releasing adequate insulin to facilitate storage, blood glucose levels rise above those observed in normal people and remain elevated for longer periods (see Table 32-3).

Glycosylated hemoglobin measures the amount of HbA_{1c} (*i.e.*, hemoglobin into which glucose has been incorporated) in the blood. When hemoglobin is released from the bone marrow, it normally does not contain glucose. During its 120-day life span in the red blood cell, hemoglobin normally becomes glycosylated to form glycohemoglobins A_{1a} and A_{1b} (2% to 4%) and A_{1c} (4% to 6%). Because glucose entry into the red blood cell is not insulin dependent, the rate at which glucose becomes attached to the hemoglobin molecule depends on blood glucose. Glycosylation is essentially irreversible, and the level of HbA_{1c} present in the blood provides an index of blood glucose levels during the previous 2 to 3 months. The ADA recommends initiating corrective measures for HbA_{1c} levels greater than 8%. However, after the United Kingdom Prospective Diabetes Study (UKPDS) study, the goal has been redefined as lowering the HbA_{1c} to less than 7.0%, or even achieving normal glycemic levels of less than 6.0%.[14]

Technologic advances have provided the means for monitoring blood glucose levels by using a drop of capillary blood. This procedure has provided health professionals with a rapid and economical means for monitoring blood glucose and has given people with diabetes a way of maintaining near-normal blood glucose levels through self-monitoring of blood glucose. Laboratory tests that use plasma for the measurement of blood glucose give results that are 10% to 15% higher than the finger stick method, which uses whole blood. Many blood glucose monitors approved for home use and some test strips now calibrate blood glucose readings to plasma values. It is important that people with diabetes know whether their monitors or glucose strips provide whole blood or plasma test results.

Urine Tests

Urine glucose tests only reflect urine glucose levels and are influenced by such factors as the renal threshold for glucose, fluid intake and urine concentration, urine testing methodologies, and some drugs. Because of these factors, the ADA recommends that all people who use insulin should self-monitor their blood glucose, not urine glucose.[13] Unlike glucose tests, urine ketone determinations remain an important part of monitoring diabetic control, particularly in people with type 1 diabetes who are at risk for developing ketoacidosis and in pregnant women with diabetes to check the adequacy of nutrition and glucose control.

Diabetes Management

The desired outcomes for management of both type 1 and type 2 diabetes is normalization of blood glucose as a means of preventing short- and long-term complications. Treatment plans usually involve nutrition therapy, exercise, and antidiabetic agents. People with type 1 diabetes require insulin therapy from the time of diagnosis. Weight loss and dietary management may be sufficient to control blood glucose levels in people with type 2 diabetes. However, they require follow-up care because insulin secretion from the beta cells may decrease or insulin resistance may persist, in which case oral antidiabetic agents are prescribed. Among the methods used to achieve these goals are education in self-management and problem solving. Individual treatment goals should take into account the person's age and other disease conditions, the person's capacity to understand and carry out the treatment regimen, and socioeconomic factors that might influence compliance with the treatment plan. Optimal control of type 2 diabetes is associated with prevention or delay of chronic diabetes complications.[15]

Dietary Management

Dietary management usually is prescribed to meet the specific needs of each person with diabetes. Goals and principles of diet therapy differ between type 1 and type 2 diabetes, as well as for lean and obese people. Integral to diabetes management is a prescribed plan for nutrition therapy.[16] Therapy goals include maintenance of near-normal blood glucose levels, achievement of optimal lipid levels, adequate calories to maintain and attain reasonable weights, prevention and treatment of chronic diabetes complications, and improvement of overall health through optimal nutrition.

For a person with type 1 diabetes, the usual food intake is assessed and used as a basis for adjusting insulin therapy to fit with the person's lifestyle. Eating consistent amounts and types of food at specific and routine times is encouraged. Home blood glucose monitoring is used to fine-tune the plan. Newer forms of therapy, such as multiple daily insulin injections and the use of an insulin pump, provide many options.

Most people with type 2 diabetes are overweight. Nutrition therapy goals focus on achieving glucose, lipid, and blood pressure goals, and weight loss if indicated. Mild to moderate weight loss (5 to 10 kg or 10 to 20 pounds) has been shown to improve diabetes control, even if desirable weight is not achieved.[17]

A coordinated team effort, including the person with diabetes, is needed to individualize the nutrition plan. The diabetic diet has undergone marked changes through the years, particularly in the recommendations for distribution of calories among carbohydrates, proteins, and fats. There no longer is a specific diabetic or ADA diet but rather a dietary prescription based on nutrition assessment and treatment goals. Information is assessed regarding metabolic parameters and medical history of factors such as renal impairment and gastrointestinal autonomic neuropathy.

Exercise

The benefits of exercise include cardiovascular fitness and psychological well-being. For many people with type 2 diabetes, the benefits of exercise include a decrease in body fat, better weight control, and improvement in insulin sensitivity.[18] In general, sporadic exercise has only transient benefits; a regular exercise or training program is the most beneficial. It is better for cardiovascular conditioning and can maintain a muscle–fat ratio that enhances peripheral insulin receptivity.

In people with insulin-dependent diabetes, the beneficial effects of exercise are accompanied by an increased risk of hypoglycemia. Although muscle uptake of glucose increases significantly, the ability to maintain blood glucose levels is hampered by failure to suppress the absorption of injected insulin and activate the counter-regulatory mechanisms that maintain blood glucose. Even after exercise ceases, insulin's lowering effect on blood glucose levels continues. In some people with type 1 diabetes, the symptoms of hypoglycemia occur many hours after cessation of exercise. People with diabetes should be aware that delayed hypoglycemia can occur after exercise and that they may need to alter their diabetes medication dose, their carbohydrate intake, or both.

Although of benefit to people with diabetes, exercise must be weighed on the risk-benefit scale. Before beginning an exercise program, persons with diabetes should undergo an appropriate evaluation for macrovascular and microvascular disease.[18] The goal of exercise is safe participation in activities consistent with an individual's lifestyle. Considerations include the potential for hypoglycemia, hyperglycemia, ketosis, cardiovascular ischemia and dysrhythmias (particularly silent ischemic heart disease), exacerbation of proliferative retinopathy, and lower extremity injury. For those with chronic diabetes, the complications of vigorous exercise can be harmful and cause eye hemorrhage and other problems. For people with type 1 diabetes who exercise during periods of poor control (*i.e.*, when blood glucose is elevated, exogenous insulin levels are low, and ketonemia exists), blood glucose and ketone levels rise to even higher levels because the stress of exercise is superimposed on pre-existing insulin deficiency and increased counter-regulatory hormone activity.

Antidiabetic Medications

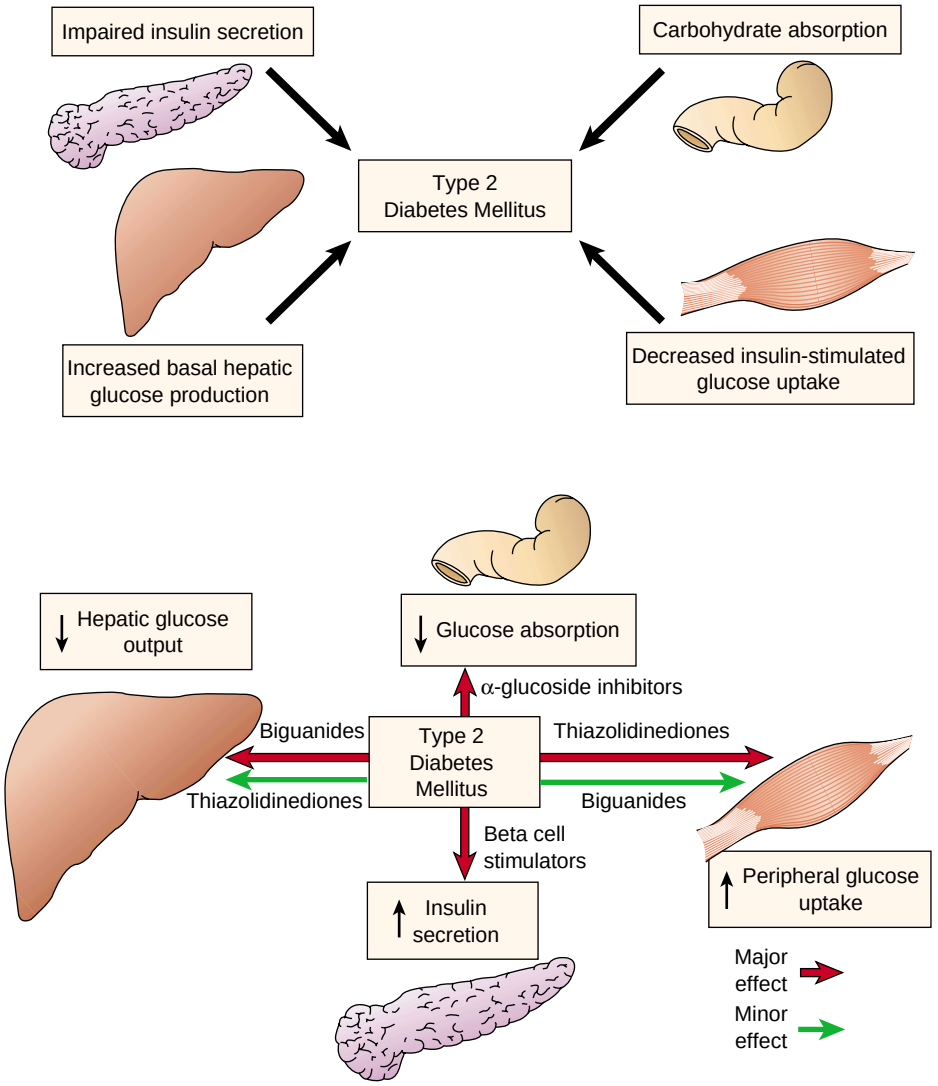
There are two categories of antidiabetic agents: insulin and oral medications. Because people with type 1 diabetes are deficient in insulin, they are in need of exogenous insulin replacement therapy from the start. People with type 2 diabetes have increased hepatic glucose production; decreased peripheral utilization of glucose; decreased utilization of ingested carbohydrates; and over time, impaired insulin secretion from the pancreas (Fig. 32-8). The oral antidiabetic agents used in the treatment of type 2 diabetes exert their action in one or sometimes all of these areas.[19] If good glycemic control cannot be achieved with a combination of oral agents, insulin can be used with the oral agents or by itself.

Insulin. Type 1 diabetes mellitus always requires treatment with insulin, and many people with type 2 diabetes eventually require insulin therapy. Insulin is destroyed in the gastrointestinal tract and must be administered by injection. Insulin preparations are categorized according to onset, peak, and duration of action. There are three principal types of insulin: short-acting, intermediate-acting, and long-acting.

Oral Antidiabetic Agents. The oral antidiabetic agents that are used in the treatment of type 2 diabetes fall into four categories: beta cell stimulators (sulfonylureas, repaglinide, and nateglinide), biguanides (Metformin), α-glucosidase inhibitors, and thiazolidinediones.[20]

The *beta cell stimulators* act at the level of the pancreatic beta cells to stimulate insulin release. They require the presence of functioning beta cells, are used only in the treatment of type 2 diabetes, and have the potential for producing hypoglycemia. The sulfonylureas reduce blood glucose by stimulating the release of insulin from beta cells in the pancreas and increasing the sensitivity of peripheral tissues to insulin. Repaglinide and nateglinide are nonsulfonylurea beta cell stimulators. These agents, which are rapidly absorbed from the gastrointestinal tract, are taken shortly before meals. Both repaglinide and nateglinide can produce hypoglycemia; thus, proper timing of meals in relation to drug administration is important.

Metformin, the only currently available biguanide, inhibits hepatic glucose production and increases the sensitivity of peripheral tissues to the actions of insulin. Secondary benefits of metformin therapy include weight loss and improved lipid



■ **FIGURE 32-8** ■ (**Top**) Mechanisms of elevated blood glucose in type 2 diabetes. (**Bottom**) Action sites of oral hypoglycemic agents and mechanisms of lowering blood glucose in type 2 diabetes mellitus.

profiles. Unlike the sulfonylureas, whose primary action is to increase insulin secretion, metformin exerts its beneficial effects on glycemic control through decreased hepatic glucose production (main effect) and increased peripheral use of glucose. This medication does not stimulate insulin secretion; therefore, it does not produce hypoglycemia. Because of the risk for lactic acidosis, metformin is contraindicated in people with elevated serum creatinine levels, clinical and laboratory evidence of liver disease, or conditions associated with hypoxemia or dehydration.

The *α-glucosidase inhibitors* block the action of the brush border enzymes in the small intestine that break down complex carbohydrates. By delaying the breakdown of complex carbohydrates, the α-glucosidase inhibitors delay the absorption of carbohydrates from the gut and blunt the postprandial increase in plasma glucose and insulin levels. The postprandial hyperglycemia probably accounts for sustained increases in HbA_{1c} levels.

The thiazolidinediones (TZDs), or glitazones, are the only class of drugs that directly target insulin resistance, a fundamental defect in the pathophysiology of type 2 diabetes. The TZDs improve glycemic control by increasing insulin sensitivity in the insulin-responsive tissues—liver, skeletal muscle, and fat—allowing the tissues to respond to endogenous insulin more efficiently without increased output from already dysfunctional beta cells. A secondary effect is the suppression of hepatic glucose production. The mechanism of action of the TZDs is complex and not fully understood but is believed to be associated with binding of the drug to a nuclear receptor that plays a role in the regulation of genes involved in lipid and glucose metabolism.[21] Because of a potential problem with liver toxicity, liver enzymes should be measured when using these drugs.

Pancreas or Islet Cell Transplantation

Pancreas or islet cell transplantation is not a lifesaving procedure. However, it does afford the potential for significantly improving the quality of life. The most serious problems are the requirement for immunosuppression and the need for diagnosis and treatment of rejection. Investigators are looking for methods of transplanting islet cells and protecting the cells from destruction without the use of immunosuppressive drugs.[24]

Acute Complications

The three major acute complications of diabetes are diabetic ketoacidosis, the hyperglycemic hyperosmolar nonketotic syndrome, and hypoglycemia. The Somogyi effect and dawn phenomenon, which result from the mobilization of counterregulatory hormones, contribute to difficulties with diabetic control.

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) occurs when ketone production by the liver exceeds cellular use and renal excretion.[25] DKA most commonly occurs in a person with type 1 diabetes, in whom the lack of insulin leads to mobilization of fatty acids from adipose tissue because of the unsuppressed adipose cell lipase activity that breaks down triglycerides into fatty acids and glycerol. The increase in fatty acid levels leads to ketone production by the liver (Fig. 32-9). It can occur at the onset of

■ **FIGURE 32-9** ■ Mechanisms of diabetic ketoacidosis.

the disease, often before the disease has been diagnosed. For example, a mother may bring a child into the clinic or emergency department with reports of lethargy, vomiting, and abdominal pain, unaware that the child has diabetes. Stress increases the release of gluconeogenic hormones and predisposes the person to the development of ketoacidosis. DKA often is preceded by physical or emotional stress, such as infection, pregnancy, or extreme anxiety. In clinical practice, ketoacidosis also occurs with the omission or inadequate use of insulin.

The three major metabolic derangements in DKA are hyperglycemia, ketosis, and metabolic acidosis. The definitive diagnosis of DKA consists of hyperglycemia (blood glucose levels >250 mg/dL), low bicarbonate (<15 mEq/L), and low pH (<7.3), with ketonemia (positive at 1:2 dilution) and moderate ketonuria.[25,26] Hyperglycemia leads to osmotic diuresis, dehydration, and a critical loss of electrolytes. Hyperosmolality of extracellular fluids from hyperglycemia leads to a shift of water and potassium from the intracellular to the extracellular compartment. Extracellular sodium concentration frequently is low or normal despite enteric water losses because of the intracellular-extracellular fluid shift. This dilutional effect is referred to as *pseudohyponatremia*. Serum potassium levels may be normal or elevated, despite total potassium depletion resulting from protracted polyuria and vomiting. Metabolic acidosis is caused by the excess ketoacids that require buffering by bicarbonate ions; this leads to a marked decrease in serum bicarbonate levels.

Compared with an insulin reaction, DKA usually is slower in onset, and recovery is more prolonged. The person typically has a history of 1 or 2 days of polyuria, polydipsia, nausea, vomiting, and marked fatigue, with eventual stupor that can progress to coma. Abdominal pain and tenderness may be experienced without abdominal disease. The breath has a characteristic fruity smell because of the presence of the volatile ketoacids. Hypotension and tachycardia may be present because of a decrease in blood volume. A number of the signs and symptoms that occur in DKA are related to compensatory mechanisms. The heart rate increases as the body compensates for a decrease in blood volume, and the rate and depth of respiration increase (*i.e.*, Kussmaul's respiration) as the body attempts to prevent further decreases in pH. Metabolic acidosis is discussed further in Chapter 6.

The goals in treating DKA are to improve circulatory volume and tissue perfusion, decrease serum glucose, correct the acidosis, and correct electrolyte imbalances. These objectives usually are accomplished through the administration of insulin and intravenous fluid and electrolyte replacement solutions. Because insulin resistance accompanies severe acidosis, low-dose insulin therapy is used. Frequent laboratory tests are used to monitor blood glucose and serum electrolyte levels and to guide fluid and electrolyte replacement. Identification and treatment of the underlying cause, such as infection, also are important.

Hyperglycemic Hyperosmolar Nonketotic Syndrome

The hyperglycemic hyperosmolar nonketotic (HHNK) syndrome is characterized by hyperglycemia (blood glucose >600 mg/dL), hyperosmolarity (plasma osmolarity >310 mOsm/L) and dehydration, the absence of ketoacidosis, and depression of the sensorium.[25] HHNK syndrome may occur in various conditions, including type 2 diabetes, acute pancreatitis, severe infection, myocardial infarction, and treatment with oral or parenteral nutrition solutions. It is seen most frequently in people with type 2 diabetes. Two factors appear to contribute to the hyperglycemia that precipitates the condition: an increased resistance to the effects of insulin and an excessive carbohydrate intake.

In hyperosmolar states, the increased serum osmolarity has the effect of pulling water out of body cells, including brain cells. The condition may be complicated by thromboembolic events arising because of the high serum osmolality. The most prominent manifestations are dehydration, neurologic signs and symptoms, and excessive thirst. The neurologic signs include grand mal seizures, hemiparesis, aphasia, muscle fasciculations, hyperthermia, visual field loss, nystagmus, and visual hallucinations. The onset of HHNK syndrome often is insidious, and because it occurs most frequently in older people, it may be mistaken for a stroke.

The treatment of HHNK syndrome requires judicious medical observation and care because water moves back into brain cells during treatment, posing a threat of cerebral edema. Extensive potassium losses that also have occurred during the diuretic phase of the disorder require correction. Because of the problems encountered in the treatment of HHNK and the serious nature of the disease conditions that cause it, the prognosis for this disorder is less favorable than that for ketoacidosis.

Hypoglycemia

Hypoglycemia, sometimes referred to as an insulin reaction, occurs from a relative excess of insulin in the blood and is characterized by below-normal blood glucose levels.[22] It occurs most commonly in people treated with insulin injections, but prolonged hypoglycemia also can result from some oral hypoglycemic agents (*i.e.*, beta cell stimulators). Many factors precipitate an insulin reaction in a person with type 1 diabetes, including error in insulin dose, failure to eat, increased exercise, decreased insulin need after removal of a stress situation, medication changes, and a change in insulin site. Alcohol decreases liver gluconeogenesis, and people with diabetes need to be cautioned about its potential for causing hypoglycemia, especially if it is consumed in large amounts or on an empty stomach.

Hypoglycemia usually has a rapid onset and progression of symptoms. Because the brain relies on blood glucose as its main energy source, hypoglycemia produces behaviors related to altered cerebral function. Headache, difficulty in problem solving, disturbed or altered behavior, coma, and seizures may occur. At the onset of the hypoglycemic episode, activation of the parasympathetic nervous system often causes hunger. The initial parasympathetic response is followed by activation of the sympathetic nervous system; this causes anxiety, tachycardia, sweating, and constriction of the skin vessels (*i.e.*, the skin is cool and clammy).

There is wide variation in the manifestation of signs and symptoms; not every person with diabetes manifests all or even most of the symptoms. The signs and symptoms of hypoglycemia are more variable in children and in elderly people. Elderly people may not display the typical autonomic responses associated with hypoglycemia but frequently have signs of impaired function of the central nervous system, including

mental confusion. Some people experience hypoglycemic unawareness. Unawareness of hypoglycemia should be suspected in people who do not report symptoms when their blood glucose concentrations are less than 50 to 60 mg/dL. This occurs most commonly in people who have a longer duration of diabetes and HbA_{1c} levels within the normal range.[23] Some medications, such as β-adrenergic–blocking drugs, interfere with the sympathetic response normally seen in hypoglycemia.

The most effective treatment of an insulin reaction is the immediate ingestion of a concentrated carbohydrate source, such as sugar, honey, candy, or orange juice. Alternative methods for increasing blood glucose may be required when the person having the reaction is unconscious or unable to swallow. Glucagon may be given intramuscularly or subcutaneously. Glucagon acts by hepatic glycogenolysis to raise blood sugar. Because the liver contains only a limited amount of glycogen (approximately 75 g), glucagon is ineffective in people whose glycogen stores have been depleted. In situations of severe or life-threatening hypoglycemia, it may be necessary to administer glucose intravenously.

The Somogyi Effect and Dawn Phenomenon

The Somogyi effect describes a cycle of insulin-induced posthypoglycemic episodes. In 1924, Joslin and associates noticed that hypoglycemia was associated with alternate episodes of hyperglycemia.[27] It was not until 1959 that Somogyi presented the results of his 20 years of studies, which confirmed the observation that "hypoglycemia begets hyperglycemia." In people with diabetes, insulin-induced hypoglycemia produces a compensatory increase in blood levels of catecholamines, glucagon, cortisol, and growth hormone. These counter-regulatory hormones cause blood glucose to become elevated and produce some degree of insulin resistance. The cycle begins when the increase in blood glucose and insulin resistance is treated with larger insulin doses. The hypoglycemic episode often occurs during the night or at a time when it is not recognized, rendering the diagnosis of the phenomenon more difficult.

Research suggests that even rather mild insulin-associated hypoglycemia, which may be asymptomatic, can cause hyperglycemia in those with type 1diabetes through the recruitment of counter-regulatory mechanisms. A concomitant waning of the effect of insulin (*i.e.*, end of the duration of action), when it occurs, exacerbates posthypoglycemic hyperglycemia and accelerates its development. These findings may explain the labile nature of the disease in some people with diabetes. Measures to prevent hypoglycemia and the subsequent activation of counter-regulatory mechanisms include a redistribution of dietary carbohydrates and an alteration in insulin dose or time of administration.[28]

The dawn phenomenon is characterized by increased levels of fasting blood glucose or insulin requirements, or both, between 5 and 9 AM without preceding hypoglycemia. It occurs in people with type 1 or type 2 diabetes. It has been suggested that a change in the normal circadian rhythm for glucose tolerance, which usually is higher during the later part of the morning, is altered in people with diabetes.[29] Growth hormone has been suggested as a possible factor. When the dawn phenomenon occurs alone, it may produce only mild hyperglycemia, but when it is combined with the Somogyi effect, it may produce profound hyperglycemia.

Chronic Complications

The chronic complications of diabetes include neuropathies, disorders of the microcirculation (*i.e.*, neuropathies, nephropathies, and retinopathies), macrovascular complications, and foot ulcers. These disorders occur in the insulin-independent tissues of the body—tissues that do not require insulin for glucose entry into the cell. This probably means that intracellular glucose concentrations in many of these tissues approach or equal those in the blood. The level of chronic glycemia is the most clearly established factor associated with diabetic complications.[14,30,31] The Diabetes Control and Complications Trial (DCCT), which was conducted with 1441 people with type 1 diabetes, has demonstrated that the incidence of retinopathy, nephropathy, and neuropathy can be reduced by intensive diabetic treatment.[32] Similar results have been demonstrated by the UKPDS in people with type 2 diabetes.[14,33]

Peripheral Neuropathies

Although the incidence of peripheral neuropathies is high among people with diabetes, it is difficult to document exactly how many people are affected by these disorders because of the diversity in clinical manifestations and because the condition often is far advanced before it is recognized. Results of the DCCT study showed that intensive therapy can reduce the incidence of clinical neuropathy by 60% compared with conventional therapy.[34,35]

Two types of pathologic changes have been observed in connection with diabetic peripheral neuropathies. The first is a thickening of the walls of the nutrient vessels that supply the nerve, leading to the assumption that vessel ischemia plays a major role in the development of these neural changes. The second finding is a segmental demyelinization process that affects the Schwann cell. This demyelinization process is accompanied by a slowing of nerve conduction.

The clinical manifestations of the diabetic peripheral neuropathies vary with the location of the lesion. Although there are several methods for classifying the diabetic peripheral neuropathies, a simplified system divides them into the somatic and autonomic nervous system neuropathies (Chart 32-1).

Somatic Neuropathy. A distal symmetric polyneuropathy, in which loss of function occurs in a stocking-glove pattern, is the most common form of somatic peripheral neuropathy. Somatic sensory involvement usually occurs first and usually is bilateral, symmetric, and associated with diminished perception of vibration, pain, and temperature, particularly in the lower extremities. In addition to the discomforts associated with the loss of sensory or motor function, lesions in the peripheral nervous system predispose a person with diabetes to other complications. The loss of feeling, touch, and position sense increases the risk of falling. Impairment of temperature and pain sensation increases the risk of serious burns and injuries to the feet.

Painful diabetic neuropathy involves the somatosensory neurons that carry pain impulse. This disorder, which causes hypersensitivity to light touch and occasionally severe "burning pain," particularly at night, can become physically and emotionally disabling.[35,36]

Autonomic Neuropathy. With autonomic nervous system neuropathies, there are defects in vasomotor responses, de-

CHART 32-1 Classification of Diabetic Peripheral Neuropathies

Somatic

Polyneuropathies (bilateral sensory)
- Paresthesias, including numbness and tingling
- Impaired pain, temperature, light touch, two-point discrimination, and vibratory sensation
- Decreased ankle and knee-jerk reflexes

Mononeuropathies
- Involvement of a mixed nerve trunk that includes loss of sensation, pain, and motor weakness

Amyotrophy
- Associated with muscle weakness, wasting, and severe pain of muscles in the pelvic girdle and thigh

Autonomic

Impaired vasomotor function
- Postural hypotension

Impaired gastrointestinal function
- Gastric atony
- Diarrhea, often postprandial and nocturnal

Impaired genitourinary function
- Paralytic bladder
- Incomplete voiding
- Impotence
- Retrograde ejaculation

Cranial nerve involvement
- Extraocular nerve paralysis
- Impaired pupillary responses
- Impaired special senses

KEY CONCEPTS

CHRONIC COMPLICATIONS OF DIABETES

- The chronic complications of diabetes result from elevated blood glucose levels and associated impairment of lipid and other metabolic pathways.
- Diabetic peripheral neuropathies, which affect both the somatic and autonomic nervous systems, result from the demyelinating effect of long-term uncontrolled diabetes.
- Diabetic nephropathy, which is a leading cause of end-stage renal disease, is associated with the increased work demands and microalbuminemia imposed by poorly controlled blood glucose levels.
- Diabetic retinopathy, which is a leading cause of blindness, is closely linked to elevations in blood glucose and hyperlipidemia seen in persons with uncontrolled diabetes.
- Macrovascular disorders such as coronary heart disease, stroke, and peripheral vascular disease reflect the combined effects of unregulated blood glucose levels, elevated blood pressure, and hyperlipidemia.
- The chronic complications of diabetes are best prevented by measures aimed at tight control of blood glucose levels, maintenance of normal lipid levels, and control of hypertension.

creased cardiac responses, impaired motility of the gastrointestinal tract, inability to empty the bladder, and sexual dysfunction.[37] Defects in vasomotor reflexes can lead to dizziness and syncope when the person moves from the supine to the standing position. Gastroparesis (impaired emptying of the stomach) can lead to alternating bouts of diarrhea, particularly at night, and constipation. Incomplete emptying of the bladder predisposes to urinary stasis and bladder infection and increases the risk of renal complications.

In the male, disruption of sensory and autonomic nervous system function may cause sexual dysfunction (see Chapter 33). Diabetes is the leading physiologic cause of erectile dysfunction, and it occurs in both type 1 and type 2 diabetes. Of the 5 million men with diabetes in the United States, 30% to 60% have erectile dysfunction. [38, 39]

Nephropathies

Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD), accounting for 40% of new cases.[1] In the United States, 33% of all people who seek renal replacement therapy (see Chapter 24) have diabetes.[40] The complication affects people with both type 1 and type 2 diabetes.

The term *diabetic nephropathy* is used to describe the combination of lesions that often occur concurrently in the diabetic kidney. The most common kidney lesions in people with diabetes are those that affect the glomeruli. Various glomerular changes may occur, including capillary basement membrane thickening, diffuse glomerular sclerosis, and nodular glomerulosclerosis (see Chapter 33).

Because not all people with diabetes experience clinically significant nephropathy, attention is focusing on risk factors for the development of this complication. Among the suggested risk factors are genetic and familial predisposition, elevated blood pressure, poor glycemic control, smoking, hyperlipidemia, and microalbuminemia.[40,41] The risk for development of ESRD also is greater among Native Americans, Hispanics (especially Mexican Americans), and African Americans.[41]

One of the first manifestations of diabetic nephropathy is an increase in urinary albumin excretion (*i.e.*, microalbuminuria), which is easily assessed by laboratory methods. Microalbuminuria is defined as a urine protein loss between 30 and 300 mg/day. The risk of microalbuminuria increases abruptly with hemoglobin A_{1c} levels greater than 8.1%.[41] Both systolic and diastolic hypertension accelerates the progression of diabetic nephropathy. Even moderate lowering of blood pressure can decrease the risk of ESRD. Smoking increases the risk of ESRD in both people with diabetes and those without the disease. People with type 2 diabetes who smoke have a greater risk of microalbuminemia, and their rate of progression to ESRD is approximately twice as rapid as in those who do not smoke.[41]

Measures to prevent diabetic nephropathy or its progression in persons with diabetes include achievement of glycemic control, maintenance of blood pressure in the midnormal range (125 to 130/75 to 85 mm Hg), prevention or reduction in the level of proteinuria, and smoking cessation in people who smoke.[40,41]

Retinopathies

Diabetes is the leading cause of acquired blindness in the United States. Although people with diabetes are at increased risk for the development of cataracts and glaucoma, retinopathy is the most common pattern of eye disease. Diabetic retinopathy is estimated to be the most common cause of newly diagnosed blindness among Americans between the ages of 20 and 74 years.[42] Diabetic retinopathy is characterized by abnormal retinal vascular permeability, microaneurysm formation, neovascularization and associated hemorrhage, scarring, and retinal detachment (see Chapter 40).[42,43] Twenty years after the onset of diabetes, nearly all people with type 1 diabetes and more than 60% of people with type 2 diabetes have some degree of retinopathy. Pregnancy, puberty, and cataract surgery can accelerate these changes.[42,43]

Although there has been no extensive research on risk factors associated with diabetic retinopathy, they appear to be similar to those for other complications. Among the suggested risk factors associated with diabetic retinopathy are poor glycemic control, elevated blood pressure, and hyperlipidemia. Because of the risk of retinopathy, it is important that people with diabetes have regular dilated eye examinations. They should have an initial examination for retinopathy shortly after the diagnosis of diabetes is made and appropriate follow-up examinations.[42]

People with macular edema, moderate to severe nonproliferative retinopathy, or any proliferative retinopathy should receive the care of an ophthalmologist. Methods used in the treatment of diabetic retinopathy include the destruction and scarring of the proliferative lesions with laser photocoagulation. The Diabetic Retinopathy Study provides evidence that photocoagulation may delay or prevent visual loss in more than 50% of eyes with proliferative retinopathy.[44]

Macrovascular Complications

Diabetes mellitus is a major risk factor for coronary artery disease, cerebrovascular disease, and peripheral vascular disease. The prevalence of these vascular complications is increased two- to fourfold in people with diabetes.

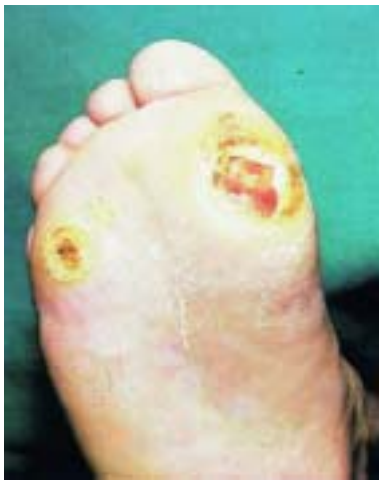
Multiple risk factors for vascular disease, including obesity, hypertension, hyperglycemia, hyperinsulinemia, hyperlipidemia, altered platelet function, and elevated fibrinogen levels, frequently are found in people with diabetes. The prevalence of coronary artery disease, stroke, and peripheral vascular disease is substantially increased in people with diabetes, even in the absence of these risk factors. There appear to be differences between type 1 and type 2 diabetes in terms of duration of disease and the development of macrovascular disease. In people with type 2 diabetes, macrovascular disease may be present at the time of diagnosis. In type 1 diabetes, the attained age and the duration of diabetes appear to correlate with the degree of macrovascular disease. The reason for these discrepancies has been attributed to the IGT that exists before the actual diagnosis of type 2 diabetes.[32,45]

Diabetic Foot Ulcers

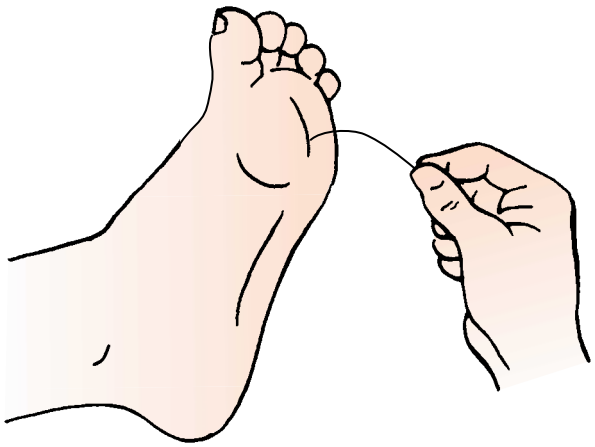
Foot problems are common among people with diabetes and may become severe enough to cause ulceration and infection, eventually resulting in amputation. Foot problems have been reported as the most common complication leading to hospitalization among people with diabetes. In a controlled study of 854 outpatients with diabetes followed up in a general medical clinic, foot problems accounted for 16% of hospital admissions during a 2-year period and 23% of total hospital days.[46] In people with diabetes, lesions of the feet represent the effects of neuropathy and vascular insufficiency. Approximately 60% to 70% of people with diabetic foot ulcers have neuropathy without vascular disease, 15% to 20% have vascular disease, and 15% to 20% have neuropathy and vascular disease.[46]

Distal symmetric neuropathy is a major risk factor for foot ulcers. People with sensory neuropathies have impaired pain sensation and often are unaware of the constant trauma to the feet caused by poorly fitting shoes, improper weight bearing, hard objects or pebbles in the shoes, or infections such as athlete's foot. Neuropathy prevents people from detecting pain; they are unable to adjust their gait to avoid walking on an area of the foot where pressure is causing trauma and necrosis. Motor neuropathy with weakness of the intrinsic muscles of the foot may result in foot deformities, which lead to focal areas of high pressure. When the abnormal focus of pressure is coupled with loss of sensation, a foot ulcer can occur. Common sites of trauma are the back of the heel, the plantar metatarsal area, or the great toe, where weight is borne during walking (Fig. 32-10).

All persons with diabetes should receive a full foot examination at least once a year. This examination should include assessment of protective sensation, foot structure and biomechanics, vascular status, and skin integrity.[47] Evaluation of neurologic function should include a somatosensory test using either the Semmes-Weinstein monofilament or vibratory sensation. The Semmes-Weinstein monofilament is a simple, inexpensive device for testing sensory status[47] (Fig. 32-11).



■ **FIGURE 32-10** ■ Neuropathic ulcers occur on pressure points in areas with diminished sensation in diabetic polyneuropathy. Pain is absent (and therefore the ulcer may go unnoticed). (Bates B.B. [1995]. *A guide to physical examination and history taking* [6th ed.]. Philadelphia: J.B. Lippincott)



■ **FIGURE 32-11** ■ Use of a monofilament in testing for impaired sensation in the foot of a person with diabetes. When the unsupported end the monofilament is pressed against the skin until it buckles or bends slightly, it delivers 10 g of pressure at the point of contact. Usually 4 and 10 sites are tested for impaired sensation.

Because of the constant risk of foot problems, it is important that people with diabetes wear shoes that have been fitted correctly and inspect their feet daily, looking for blisters, open sores, and fungal infection (*e.g.*, athlete's foot) between the toes. If their eyesight is poor, a family member should do this for them. In the event a lesion is detected, prompt medical attention is needed to prevent serious complications. Specially designed shoes have been demonstrated to be effective in preventing relapses in people with previous ulcerations. Smoking should be avoided because it causes vasoconstriction and contributes to vascular disease. Because cold produces vasoconstriction, appropriate foot coverings should be used to keep the feet warm and dry. Toenails should be cut straight across to prevent ingrown toenails. The toenails often are thickened and deformed, requiring the services of a podiatrist.

Infections

Although not specifically an acute or a chronic complication, infections are a common concern of people with diabetes. Certain types of infections occur with increased frequency in people with diabetes: soft tissue infections of the extremities, osteomyelitis, urinary tract infections and pyelonephritis, candidal infections of the skin and mucous surfaces, dental caries and infections, and tuberculosis.[48] Controversy exists about whether infections are more common in people with diabetes or whether infections seem more prevalent because they often are more serious in people with diabetes.

Suboptimal response to infection in a person with diabetes is caused by the presence of chronic complications, such as vascular disease and neuropathies, and by the presence of hyperglycemia and altered neutrophil function. Sensory deficits may cause a person with diabetes to ignore minor trauma and infection, and vascular disease may impair circulation and delivery of blood cells and other substances needed to produce an adequate inflammatory response and effect healing. Pyelonephritis and urinary tract infections are relatively common in persons with diabetes, and it has been suggested that these infections may bear some relation to the presence of a neurogenic bladder or nephrosclerotic changes in the kidneys. Hyperglycemia and glycosuria may influence the growth of microorganisms and increase the severity of the infection. Diabetes and elevated blood glucose levels also may impair host defenses such as the function of neutrophils and immune cells. Polymorphonuclear leukocyte function, particularly adherence, chemotaxis, and phagocytosis, are depressed in persons with diabetes, particularly those with poor glycemic control.

In summary, diabetes mellitus is a disorder of carbohydrate, protein, and fat metabolism resulting from an imbalance between insulin availability and insulin need. The disease can be classified as type 1 diabetes, in which there is destruction of beta cells and an absolute insulin deficiency, or type 2 diabetes, in which there is a lack of insulin availability or effectiveness. Type 1 diabetes can be further subdivided into type 1A immune-mediated diabetes, which is thought to be caused by autoimmune mechanisms, and type 1B idiopathic diabetes, for which the cause is unknown. Other specific types of diabetes include secondary forms of carbohydrate intolerance, which occur secondary to some other condition that destroys beta cells (*e.g.*, pancreatic disorders) or endocrine diseases that cause increased production of glucose by the liver and decreased use of glucose by the tissues (*e.g.*, Cushing's syndrome). GDM develops during pregnancy, and although glucose tolerance often returns to normal after childbirth, it indicates an increased risk for the development of diabetes.

The diagnosis of diabetes mellitus is based on clinical signs of the disease, fasting blood glucose levels, random plasma glucose measurements, and results of the glucose tolerance test. Self-monitoring provides a means of maintaining near-normal blood glucose levels through frequent testing of blood glucose and adjustment of insulin dosage. Glycosylation involves the irreversible attachment of glucose to the hemoglobin molecule; the measurement of HbA_{1c} provides an index of blood glucose levels during a period of several months.

The treatment of diabetes includes diet, exercise, and in many cases, the use of an antidiabetic agent. Dietary management focuses on maintaining a well-balanced diet, controlling calories to achieve and maintain an optimum weight, and regulating the distribution of carbohydrates, proteins, and fats. Two types of antidiabetic agents are used in the management of diabetes: injectable insulin and oral diabetic drugs. Type 1 diabetes, and sometimes type 2, requires treatment with injectable insulin. Oral diabetic drugs include the beta-cell–stimulating agents, biguanides, α-glucosidase inhibitors, and TZDs. These drugs require a functioning pancreas and may be used in the treatment of type 2 diabetes.

The metabolic disturbances associated with diabetes affect almost every body system. The acute complications of diabetes include hypoglycemia in insulin-treated diabetics, diabetic ketoacidosis, and hyperosmolar hyperglycemic nonketotic syndrome. The chronic complications of diabetes affect the non–insulin-dependent tissues, including the retina, blood vessels, kidneys, peripheral nervous system, and feet.

REVIEW QUESTIONS

- Characterize the actions of insulin with reference to glucose, fat, and protein metabolism.
- Explain what is meant by *counter-regulatory hormones*, and describe the actions of glucagon, epinephrine, growth hormone, and the adrenal cortical hormones in regulation of blood glucose levels.
- Compare the distinguishing features of type 1 and type 2 diabetes mellitus; list causes of other specific types of diabetes; and cite the criteria for gestational diabetes.
- Relate the physiologic functions of insulin to the manifestations of diabetes mellitus.
- Discuss the role of diet and exercise in the management of diabetes mellitus.
- Compare the pathophysiology and clinical manifestations of diabetic ketoacidosis and their physiologic significance.
- Describe the clinical manifestations of insulin-induced hypoglycemia and state how these may differ in elderly people.
- Describe alterations in physiologic function that accompany diabetic peripheral neuropathy, retinopathy, and nephropathy.
- Describe the causes of foot ulcers in people with diabetes mellitus.
- Explain the relation between diabetes mellitus and infection.

connection

Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.

REFERENCES

1. American Diabetes Association. (2000). Diabetes facts and figures. [On-line]. Available: http://www.diabetes.org/.
2. Guyton A., Hall J.E. (2000). *Textbook of medical physiology* (10th ed., pp. 884–898). Philadelphia: W.B. Saunders.
3. Shepard P.R., Kahn B. (1999). Glucose transporters and insulin action. *New England Journal of Medicine* 341, 248–256.
4. Goldfine I.R., Youngren J.F. (1998). Contributions of the *American Journal of Physiology* to the discovery of insulin. *American Journal of Physiology* 274, E207–E209.
5. Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. (1997). Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20, 1183–1199.
6. Atkinson M.A., Eisenbarth G.S. (2001). Type 1 diabetes: New perspectives on disease pathogenesis and treatment. *The Lancet* 358, 221–229.
7. Davidson M.B. (1995). Clinical implications of insulin resistance syndromes. *American Journal of Medicine* 99, 420–426.
8. Boder G. (2001). Free fatty acids—the link between obesity and insulin resistance. *Endocrine Practice* 7, 44–51.
9. Guven S., El-Bershawi A., Sonnenberg G.E., et al. (1999). Persistent elevation in plasma leptin level in ex-obese with normal body mass index: Relation to body composition and insulin sensitivity. *Diabetes* 48, 347–352.
10. Winter W.E., Kamura M., House D.W. (1999). Monogenic diabetes mellitus in youth: The MODY syndrome. *Metabolic Clinics of North America* 28, 765–785.
11. American Diabetes Association. (2000). Gestational diabetes mellitus. *Diabetes Care* 23 (Suppl. 1), S77–S79.
12. Kjos S.L., Buckanan T.A. (1999). Gestational diabetes mellitus. *New England Journal of Medicine* 341, 1749–1756.
13. American Diabetes Association. (2000). Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 23 (Suppl. 1), S14.
14. UKPDS Group. (1998). Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352, 837–853.
15. Shichiri M., Kishikquq H., Ohkubo Y., et al. (2000). Long-term results of Kumamoto Study on optimal diabetes control in type 2 diabetes patients. *Diabetes Care* 23 (Suppl. 2), B21–B29.
16. American Diabetes Association. (2000). Nutrition recommendations and principles for people with diabetes mellitus (Position Statement). *Diabetes Care* 23 (Suppl. 1), S43–S46.
17. Markovic T.P., Jenkins A.B., Campbell L.U., et al. (1998). The determinants of glycemic responses to diet restriction and weight loss and obesity in NIDDM. *Diabetes Care* 21, 687–694.
18. American Diabetes Association. (2000). Diabetes mellitus and exercise. *Diabetes Care* 23 (Suppl. 1), S50–S54.
19. Lebovitz H.E. (1999). Insulin secretogogues: Old and new. *Diabetes Reviews* 7, 139–153.
20. Vaaler S. (2000). Optimal glycemic control in type 2 diabetes patients. *Diabetes Care* 23 (Suppl. 2), B30.
21. Schoonjans J., Auwerx J. (2000). Thiazolidinediones: An update. *Lancet* 355, 1008–1010.
22. Shapiro J., Lakey J., Ryan E., et al. (2000). Islet transplantation with type 1 diabetes mellitus using glucocorticoid-free immunosuppressive regimen. *New England Journal of Medicine* 343, 230–238.
23. Herbel G., Boyle P.J. (2000). Hypoglycemia. *Endocrinology and Metabolic Clinics of North America* 29, 725–740.
24. Bolli G.B., Fanelli C.G. (1995). Unawareness of hypoglycemia. *New England Journal of Medicine* 333, 1771–1772.
25. Kitabachi A.E., Umpierrez G.E., Murphy M.B., et al. (2001). Management of hyperglycemic crisis in patients with diabetes. *Diabetes Care* 24, 131–153.
26. Delaney M.F., Zisman A., Kettyle W.M. (2000). Diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic syndrome. *Endocrinology and Metabolic Clinics of North America* 29, 725–740.
27. Somogyi M. (1957). Exacerbation of diabetes in excess insulin action. *American Journal of Medicine* 26, 169–191.
28. Bolli G.B., Gotterman I.S., Campbell P.J. (1984). Glucose counterregulation and waning of insulin in the Somogyi phenomenon (posthypoglycemic hyperglycemia). *New England Journal of Medicine* 311, 1214–1219.
29. Bolli G.B., Gerich J.E. (1984). The dawn phenomenon: A common occurrence in both non-insulin and insulin dependent diabetes mellitus. *New England Journal of Medicine* 310, 746–750.
30. Klein R., Klein B.E.K., Moss S.E. (1996). Relation of glycemic control to diabetic microvascular complications in diabetes mellitus. *Annals of Internal Medicine* 124, 90–96.
31. Estacio R.O., Jeffero B.W., Gifford N., et al. (2000). Effect of blood pressure control on diabetic neovascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 23 (Suppl. 2), B54–B64.
32. The Diabetes Control and Complications Trial Research Group. (1993). The effect of intensified treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine* 329, 955–977.
33. Stratton I.M., Adler A.I., Neil H.A., et al. (2000). Association of glycaemia with macrovascular and microvascular complications in type 2 diabetes (UKPDS 35) Group: Prospective observational study. *British Medical Journal* 321, 405–412.
34. Said G. (1996). Diabetic neuropathy: An update. *Neurology* 243, 431–440.
35. Vinik A.I., Milicevik Z. (1996). Recent advances in the diagnosis and treatment of diabetic neuropathy. *Endocrinologist* 6, 443–461.

36. Dejaard A. (1998). Pathophysiology and treatment of diabetic neuropathy. *Diabetic Medicine* 15, 97.
37. Vinik A.I. (1999). Diabetic neuropathy: Pathogenesis and therapy. *American Journal of Medicine* 107 (Suppl. 2B), 17S–26S.
38. Spoilett G.R. (1999). Assessment and management of erectile dysfunction in men with diabetes. *Diabetes Educator* 25 (1), 65–73.
39. Lipshultz L.I. (1999). Treatment of erectile dysfunction in men. *Journal of the American Medical Association* 281, 465–466.
40. American Diabetes Association. (2000). Diabetic nephropathy. *Diabetes Care* 23 (Suppl. 1), S69–S72.
41. Ritz E., Orth S.R. (1999). Nephropathy in patients with type 2 diabetes mellitus. *New England Journal of Medicine* 341, 1127–1133.
42. Krolewski A.S., Laffel L.M.B., Krolewski M., et al. (1995). Glycosylated hemoglobin and the risk of microalbuminemia in patients with insulin-dependent diabetes mellitus. *New England Journal of Medicine* 332, 1251–1255.
43. American Diabetes Association. (2000). Diabetic retinopathy. *Diabetes Care* 23 (Suppl. 1), S73–S76.
44. Aiello L.P., Gardner T.W., King G.L., et al. (1998). Diabetic retinopathy (Technical Review). *Diabetes Care* 21, 143–156.
45. Chen Y.-D.I., Reaven G.M. (1997). Insulin resistance and atherosclerosis. *Diabetes Reviews* 5, 331–342.
46. American Diabetes Association. (2000). Preventative foot care in people with diabetes. *Diabetes Care* 23 (Suppl. 1), S55–S56.
47. Levin M.E. (1995). Preventing amputations in patients with diabetes. *Diabetes Care* 18, 1384–1394.
48. Joshi N., Caputo G.M., Weitekamp M.R., et al. (1999). Infections in patients with diabetes mellitus. *New England Journal of Medicine* 341, 1906–1912.
49. (2000). A simple screen for diabetic foot neuropathy. *Emergency Medicine* 4, 23–25.