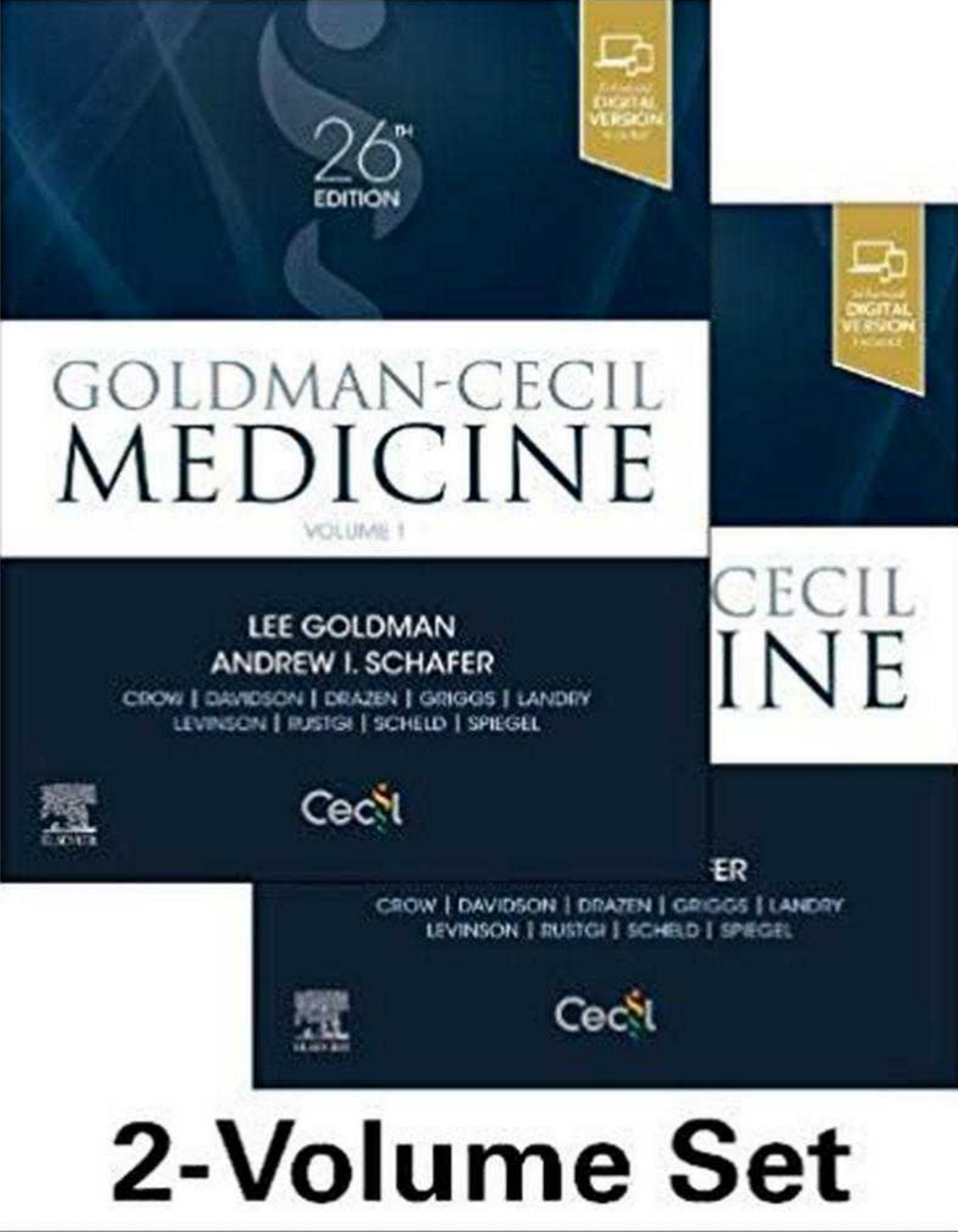
26TH EDITION
DIGITAL VERSION
GOLDMAN-CECIL
MEDICINE
VOLUME 1
LEE GOLDMAN
ANDREW I. SCHAFER
CROW | DAVIDSON | DRAZEN | GRIGGS | LANDRY
LEVINSON | RUSTGI | SCHELD | SPIEGEL
Cecil
CECIL
INE
ER
CROW | DAVIDSON | DRAZEN | GRIGGS | LANDRY
LEVINSON | RUSTGI | SCHELD | SPIEGEL
Cecil
2-Volume Set

GOLDMAN-CECIL MEDICINE

26TH EDITION

Volume 1

EDITED BY

LEE GOLDMAN, MD

Harold and Margaret Hatch Professor
Chief Executive, Columbia University Irving Medical Center
Dean of the Faculties of Health Sciences and Medicine
Columbia University
New York, New York

ANDREW I. SCHAFER, MD

Professor of Medicine
Director, Richard T. Silver Center for Myeloproliferative Neoplasms
Weill Cornell Medical College
New York, New York

ELSEVIER

Elsevier
1600 John F. Kennedy Blvd.
Ste 1600
Philadelphia, PA 19103-2899

GOLDMAN-CECIL MEDICINE, TWENTY-SIXTH EDITION
ISBN: 978-0-323-53266-2
Volume 1 ISBN: 978-0-323-76018-8
Volume 2 ISBN: 978-0-323-76019-5

INTERNATIONAL EDITION
ISBN: 978-0-323-64033-6
IE Volume 1 ISBN: 978-0-323-75998-4
IE Volume 2 ISBN: 978-0-323-75999-1

Library of Congress Control Number: 2019909209

Publishing Director, Medical Reference: Dolores Meloni
Content Development Manager: Laura Schmidt
Publishing Services Manager: Catherine Jackson
Senior Project Manager: Daniel Fitzgerald
Designer: Maggie Reid

Printed in the United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2 1

216 DIABETES MELLITUS

JILL P. CRANDALL AND HARRY SHAMOON

Diabetes mellitus is a chronic disorder characterized by abnormal metabolic regulation as well as by the potential for vascular and neuropathic complications. Diabetes comprises a cluster of heterogeneous disorders with elevated blood glucose levels as a common diagnostic feature; however, as genetic and molecular studies have suggested, it is likely that the cluster includes many subcategories, each of which requires tailored prevention, diagnosis, and treatment approaches. Depending on the context in which the patient presents, diabetes can be an acute life-threatening condition, a pregnancy-associated disorder, or a gradually evolving chronic disorder that carries with it secondary complications that may be ultimately more debilitating than hyperglycemia. Other factors make diabetes an unusual clinical challenge, including the need for active participation by patients in their treatment, the varying presentations across the age spectrum, and the unstable and evolving clinical presentation. Because the severity of the underlying metabolic defects does not remain static, diabetes management always requires changes in treatment according to the stage of the disease. These patterns of evolution are superimposed on the phenotypes at presentation and depend on a host of factors, including age, sex, race, societal setting, and others.

It is now established that diabetes-related vascular and neuropathic complications stem from imperfect treatment of the metabolic disturbances, defined principally by hyperglycemia. There is also evidence that genetic factors may predispose or protect individual patients from the deleterious effects of hyperglycemia. Regardless of the specific subtype of diabetes, all have in common some degree of insulin deficiency; insulin deficiency may be absolute, as in type 1 diabetes, or a relative deficit with coexisting insulin resistance, as in type 2 diabetes. Deficient insulin is the primary driver of impaired fuel homeostasis, whereas hyperglycemia plays the dominant role in disease-related complications. Major strides in our understanding of diabetes have been made during the last 40 years, with accompanying additions to the diagnostic and treatment armamentarium.

DEFINITIONS

Despite the heterogeneity of phenotypes, it is possible to generally classify diabetes into two major subgroups, type 1 (previously referred to as juvenile-onset or insulin-dependent diabetes) and type 2 (previously referred to as adult-onset or non–insulin-dependent diabetes). The major clinical features of type 1 and type 2 are shown in Table 216-1 and are described in detail in the corresponding sections later.

In addition to these two large categories, diabetes may occur in association with other disorders, with use of certain medications, or, rarely, as a result of a specific genetic mutation, such as maturity-onset diabetes of youth (MODY).

TABLE 216-1 CLASSIFICATION OF DIABETES

	TYPE 1	TYPE 2
Age at onset	Childhood or early adulthood, but can be manifested at any age	Middle age or older, but can be manifested in obese children and adolescents
Family history/genetic factors	Genetic risk defined, but most cases are sporadic	Strong genetic component, polygenic in most cases
Environmental triggers	Largely unknown	Obesity, sedentary lifestyle
Requirement for insulin therapy	Universal	Variable
Frequency among people with diabetes	5-10%	≈90%
Associated disorders	Autoimmunity, especially thyroid, other endocrine disorders	Hypertension, dyslipidemia, metabolic syndrome, polycystic ovary syndrome

DIABETES ASSOCIATED WITH OTHER DISORDERS OR SYNDROMES

Diabetes may occur as part of several inherited syndromes, including the Turner, Klinefelter, Prader-Willi, Down, and Wolfram syndromes, among others. The genetic and metabolic defects involved are heterogeneous but usually result in impaired β-cell function. The obesity (and resulting insulin resistance) associated with many of these syndromes also contributes. Diseases of the exocrine pancreas, such as pancreatitis, pancreatic cancer, hemochromatosis, and cystic fibrosis, can be accompanied by impaired pancreatic endocrine function, leading to insulin-deficient diabetes. Several endocrinopathies that are associated with insulin resistance, including acromegaly, Cushing syndrome, and pheochromocytoma, may result in impaired glucose tolerance or frank diabetes in predisposed individuals. Viral infections, such as congenital rubella and cytomegalovirus, may cause diabetes by β-cell destruction. Finally, hyperglycemia may be associated with the use of certain drugs, including those that worsen insulin resistance (e.g., glucocorticoids, nicotinic acid, thiazide diuretics) and those that impair β-cell function (e.g., pentamidine, diazoxide, interferon gamma).

DIAGNOSTIC CRITERIA FOR DIABETES

Diabetes is diagnosed on the basis of one of several criteria, including fasting plasma glucose concentration, plasma glucose concentration after a standard 75-g oral glucose challenge (oral glucose tolerance test), and percentage of glycosylated hemoglobin (HbA_{1c}) (Table 216-2). In most cases, abnormal results require a confirmatory test, but diabetes can be diagnosed in the presence of unequivocal hyperglycemia (casual plasma glucose concentration >200 mg/dL) and typical symptoms of polyuria, polydipsia, and weight loss.

Because plasma glucose levels range on a continuum, the selection of a specific diagnostic threshold is in some respects arbitrary. Current criteria are based on the plasma glucose or HbA_{1c} level above which the risk of diabetes-specific microvascular complications (e.g., retinopathy) is perceptibly increased. In situations of altered red blood cell turnover or certain hemoglobinopathies, HbA_{1c} may not accurately reflect mean plasma glucose levels (see later section on glycosylated hemoglobin), and direct glucose measurement should be used. Separate glucose criteria exist for the diagnosis of gestational diabetes (see section on gestational diabetes under clinical manifestations of type 2 diabetes).

States of impaired glucose regulation, not meeting the criteria for diabetes, have also been defined (fasting glucose concentration of 100 to 125 mg/dL, 2-hour glucose concentration of 140 to 199 mg/dL, or HbA_{1c} level of 5.7 to 6.4%). Individuals in these categories are at increased risk for diabetes, although not all will progress and some may revert to normal glucose regulation. Impaired glucose tolerance (oral glucose tolerance test 2-hour glucose concentration of 140 to 199 mg/dL) has also been associated with increased risk of atherosclerotic cardiovascular disease (CVD), which may be independent of future development of diabetes.

Glycosylated Hemoglobin

Measurements of glycosylated hemoglobin have been in clinical use since the 1980s as a means of assessing glucose control in patients with diabetes and more recently for the diagnosis of diabetes and pre-diabetic states. Hemoglobin A_{1c} (HbA_{1c}) is formed by the nonenzymatic glycosylation of hemoglobin, and its percentage reflects the exposure of the hemoglobin A molecule to glucose during the lifespan of circulating red blood cells (about 120 days). Thus HbA_{1c} has a predictable (but nonlinear) relationship with mean plasma glucose levels during the preceding 3 to 4 months, although more recent glucose exposure

TABLE 216-2 DIAGNOSTIC CRITERIA FOR DIABETES

	NORMAL	IMPAIRED (PRE-DIABETES)	DIABETES
Fasting glucose concentration (mg/dL)	<100	100-125	≥126
OGTT 2-hour glucose concentration (mg/dL)	<140	140-199	≥200
HbA_{1c} (%)	<5.7	5.7-6.4	≥6.5

OGTT = oral glucose tolerance test.
Modified from American Diabetes Association Standards of Medical Care in Diabetes—2018. *Diabetes Care* 2018;41(Suppl 1):S13-S27.

ABSTRACT

Diabetes mellitus is a chronic disorder characterized by elevated blood glucose, which occurs as a consequence of insulin deficiency and, in some cases, impaired insulin action. Although heterogeneous, diabetes can be separated into two broad categories. Type 1 diabetes results from autoimmune destruction of pancreatic beta cells and results in total (or near total) insulin deficiency. Type 2 diabetes is strongly associated with obesity and is characterized by relative insulin deficiency and variable defects in insulin sensitivity. Chronic hyperglycemia from all forms of diabetes can result in microvascular complications (retinopathy, nephropathy, neuropathy), as well as increased risk for atherosclerotic cardiovascular disease. Aggressive control of hyperglycemia and related risk factors, which includes medical nutrition therapy, exercise, weight management, and medications, can substantially reduce the risk of complications. Treatment of type 1 diabetes requires physiologic insulin replacement using multiple daily injections or a continuous subcutaneous insulin infusion pump. Pharmacologic options for treating type 2 diabetes include several classes of oral and injectable medications, which are often used in combination in order to achieve and maintain adequate glucose control. Acute, life-threatening complications of diabetes can occur and include diabetic ketoacidosis, hyperglycemic hyperosmolar state, and iatrogenic hypoglycemia. Recent advances in technology, including continuous glucose monitors, and availability of newer pharmacologic agents have improved quality of life for many patients with diabetes and have the potential to reduce the burden of the disease.

KEYWORDS

diabetes mellitus
type 1 diabetes
type 2 diabetes
diabetic retinopathy
diabetic nephropathy
diabetic neuropathy
ketoacidosis
hyperglycemic hyperosmolar state
hypoglycemia

(preceding 4 weeks) contributes relatively more to glycosylation. The relationship between HbA_{1c} and mean glucose levels was initially based on data obtained from the Diabetes Control and Complications Trial (DCCT) and recently updated on the basis of data obtained from studies using continuous glucose monitoring in ambulatory individuals, including those with and without diabetes (Table 216-3).

Although several different types of assays (e.g., affinity chromatography, immunoassay) are used to measure HbA_{1c}, most methods have been harmonized to a common standard and generally allow results from different laboratories to be used interchangeably. HbA_{1c} results may be influenced by a number of factors, including conditions that alter red cell survival (e.g., hemolytic anemia) or cause interference with a specific assay. In these situations, measurement of fructosamine (a glycosylated serum protein) or glycated albumin, both of which reflect mean glucose levels during the preceding 2 to 3 weeks, may provide more accurate assessment of recent glucose levels. However, these assays have not been as well standardized, and the relationship with mean plasma glucose levels is less well established.

PATHOBIOLOGY OF DIABETES

Figure 216-1 summarizes the effects of insulin deficiency on body fuel metabolism.

Given the dominant role of insulin in carbohydrate metabolism, it is not surprising that its availability and effectiveness play a role in every form of diabetes. However, because many other diabetogenic factors can be operative and there is interdependence among many of these homeostatic mechanisms, teasing out their individual contributions is virtually impossible in any given patient.

Normal insulin physiology is orchestrated in a complex dynamic involving metabolic fuels, neurotransmitters, and other hormones. Insulin is synthesized as preproinsulin in the ribosomes of the rough endoplasmic reticulum of pancreatic islet β cells and is then converted to proinsulin, which in turn is transported to the Golgi apparatus, where it is packaged into secretory granules. Proinsulin is cleaved into equimolar amounts of insulin and a connecting segment (C-peptide) in the secretory granules. The stimulation of insulin secretion results in release of equimolar quantities of insulin and C-peptide (as well as a small amount of proinsulin) into the hepatic portal vein. Whereas a large proportion of insulin is bound to its hepatic receptor and metabolized in its "first pass" through the liver, C-peptide is much less prone to hepatic metabolism and is a better reflection of insulin secretion, although it is quantitatively of limited usefulness in the clinical diagnosis or treatment of diabetes.

The principal regulator of insulin secretion is glucose. The process of β-cell insulin secretion is shown schematically in Figure 216-2. Glucose is taken up by the β cells through the GLUT2 glucose transporter system and then phosphorylated to glucose 6-phosphate by an islet-specific glucokinase. Thus glucokinase can be considered the "glucose sensor" of the β cell; mutations in this enzyme can lead to a specific diabetes syndrome (MODY2), and there is evidence of its role in common forms of type 2 diabetes. The conversion of glucose to glucose 6-phosphate results in a sequential increase in intracellular adenosine triphosphate (ATP), closing of the ATP-dependent potassium (K_{ATP}) channels in the β-cell membrane, membrane depolarization and influx of calcium, migration of the insulin secretory granules to the cell membrane and their fusion with the membrane, and finally release of insulin into the extracellular fluid. The K_{ATP} channel is made up of the sulfonylurea 1 receptor (SUR1) and an inward potassium channel subunit, Kir6.2. Mutations in either the SUR1 gene or the Kir6.2 gene lead to loss of K_{ATP} activity; as a result, the cell is depolarized, resulting in chronic release of insulin and a syndrome termed *persistent hyperinsulinemic hypoglycemia of infancy*. Mutations in Kir6.2 and SUR1 have also been identified in patients with permanent neonatal diabetes mellitus; treatment with sulfonylurea can normalize insulin secretion in these patients.

The magnitude of the insulin secretory response is determined by the level of blood glucose as well as by the rate and mode of glucose entry. Compared with intravenous administration of glucose, higher insulin levels are produced when glucose is taken orally because of the simultaneous release of gut-derived incretins that include glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), both of which augment insulin secretion. In

TABLE 216-3 THE RELATIONSHIP BETWEEN HBA_{1C} AND ESTIMATED AVERAGE GLUCOSE LEVELS DURING THE PRECEDING 3 MONTHS

	ESTIMATED AVERAGE GLUCOSE LEVEL	
HbA_{1c} (%)	**mg/dL**	**mmol/L**
5	97	5.4
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

From Nathan DM, Kuenen J, Borg R, et al. Translating the A1c assay into estimated average glucose values. *Diabetes Care*. 2008;31:1473-1478.

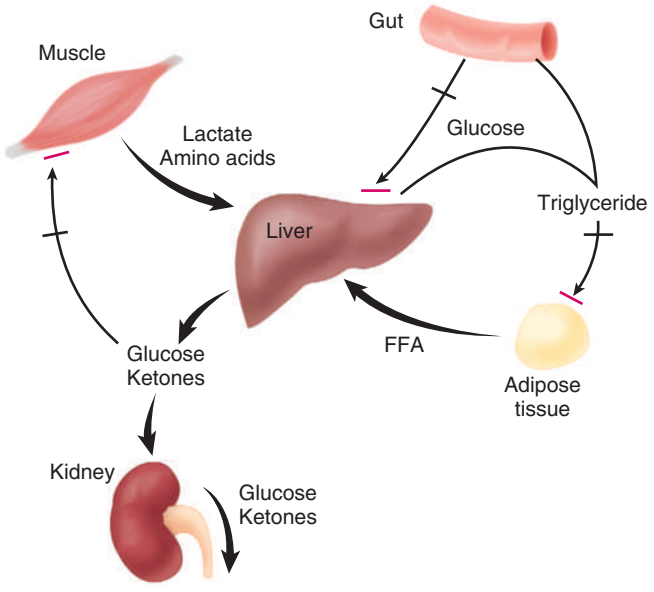

FIGURE 216-1. Effects of insulin deficiency on body fuel metabolism. Lack of insulin leads to mobilization of substrates for gluconeogenesis and ketogenesis from muscle and adipose tissue, accelerated production of glucose and ketones by the liver, and impaired removal of endogenous and exogenous fuels by insulin-responsive tissues. The net results are severe hyperglycemia and hyperketonemia that overwhelm renal removal mechanisms. FFA = free fatty acids.

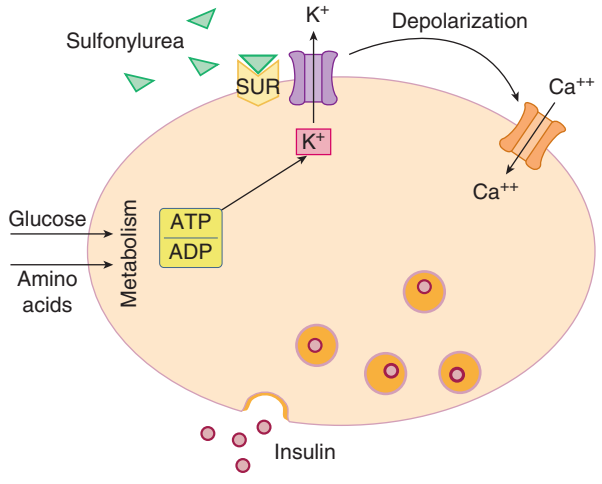

FIGURE 216-2. Nutrient regulation of insulin secretion. Glucose is taken up by the β cell through the GLUT2 glucose transporter and is metabolized (initially through phosphorylation by the glucokinase to glucose 6-phosphate). This leads to an increase in intracellular ATP (and an increase in the cytoplasmic ATP/ADP ratio), which causes closure of the ATP-dependent potassium channel, followed by membrane depolarization and the subsequent opening of voltage-gated calcium channels. The influx of calcium mobilizes the insulin secretory granules to fuse with the cell membrane and to release insulin into the extracellular fluid. The sulfonylurea 1 receptor (SUR1) is a component of the ATP-dependent potassium channel. ADP = adenosine diphosphate; ATP = adenosine triphosphate.

TABLE 216-4 THE METABOLIC EFFECTS OF INSULIN

METABOLIC EFFECT	STIMULATED BY INSULIN	INHIBITED BY INSULIN
Carbohydrate metabolism	Glucose transport Glycolysis Glycogen synthesis	Glycogen breakdown Gluconeogenesis
Protein metabolism	Amino acid transport Protein synthesis	Protein breakdown
Lipid metabolism	Triglyceride uptake Lipogenesis	Lipolysis Fatty acid oxidation

fact, drugs that mimic or enhance this incretin effect are useful in the treatment of type 2 diabetes.

Rapid increases in blood glucose concentration (e.g., after intravenous administration of glucose) cause a spike of insulin secretion that peaks within a few minutes and declines quickly (so-called first-phase insulin secretion). With more persistent elevations of plasma glucose concentration, insulin secretion is sustained (so-called second-phase insulin secretion). The earliest pathophysiologic indicator of defective β-cell function may be the loss of first-phase secretion of insulin, which precedes by years the decline in insulin secretory reserve sufficient to lead to overt glucose intolerance or diabetes.

Insulin Action

The actions of insulin on its principal target organs (i.e., muscle, fat, liver) have complex and coordinated effects on the metabolism of carbohydrates, proteins, and lipids and are mediated by its interaction with the insulin receptor. Insulin receptor signaling through insulin receptor substrate 1 and phosphatidylinositol 3-kinase is a major pathway in the mediation of insulin-stimulated glucose transport, notably by stimulating the translocation of the glucose transporter GLUT4 to the cell membrane. This pathway is also responsible for the vasodilator effects of insulin (through increased expression of endothelial nitric oxide synthase), which may contribute to glucose utilization by increasing nutrient delivery to tissues. Defects in these intracellular signaling pathways are an important cause of impaired insulin action, or "insulin resistance" (see section on impaired insulin action [insulin resistance] under pathobiology of type 2 diabetes).

The overall actions of insulin tend to promote uptake and storage of nutrients in the fed state and release of nutrients from body stores in the fasting state, as summarized in Table 216-4.

In the *postprandial period*, rising glucose levels simultaneously trigger insulin secretion and suppress glucagon release. The resulting rise in the insulin-to-glucagon ratio increases hepatic glycogen synthesis and inhibits release of glucose from the liver. Insulin stimulates glucose uptake into skeletal muscle and adipose tissue, promoting the synthesis of protein and triglycerides. In the *fasting state*, declining glucose levels inhibit insulin release, thereby increasing glycogenolysis and gluconeogenesis and the resulting delivery of glucose into the circulation. In states of absolute or relative insulin deficiency, inadequate basal insulin levels allow unrestrained hepatic glucose production, which results in fasting hyperglycemia. Inadequate insulin in the fed state impedes peripheral (predominantly skeletal muscle) glucose uptake, thereby contributing to postprandial hyperglycemia. Impaired suppression of hepatic glucose production also contributes to postprandial hyperglycemia in patients with diabetes (see also the section on type 2 diabetes).

TYPE 1 DIABETES

Epidemiology

Type 1 diabetes may be manifested at any age but most typically appears in childhood, especially around puberty. However, new cases of type 1 diabetes can appear at any time in life, and in the United States approximately 30% of patients are diagnosed after young adulthood.[1]

Worldwide, the incidence of type 1 diabetes varies 50- to 100-fold, with the highest rates occurring in individuals of northern European descent. Both sexes are equally affected in childhood, but men are affected more commonly in early adult life. The incidence of childhood type 1 diabetes is rising rapidly in all populations, especially in the age group younger than 5 years, with a doubling time of less than 20 years in Europe. In the United States, the incidence of type 1 diabetes among youth significantly increased in a linear fashion by 1.8% annually between 2002 and 2012, particularly among youths of minority

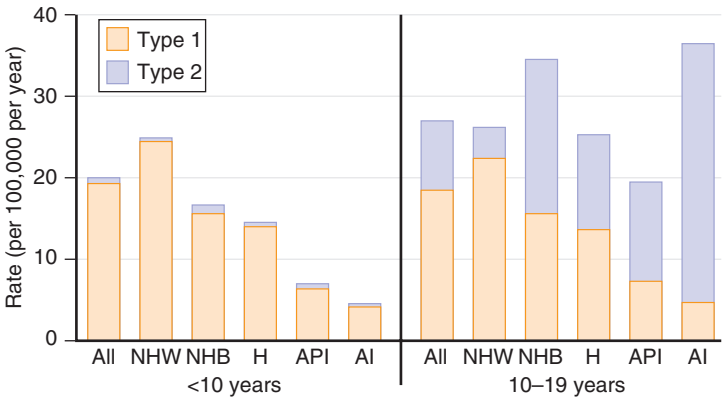

FIGURE 216-3. Rate of new cases of type 1 and type 2 diabetes among people younger than 20 years in the United States, by age and race/ethnicity, 2008–2009. AI = American Indians; API = Asian/Pacific Islander Americans; H = Hispanics/Latinos; NHB = non-Hispanic blacks; NHW = non-Hispanic whites. (From Centers for Disease Control and Prevention. *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*. Atlanta, GA: US Department of Health and Human Services; 2014. Source: SEARCH for Diabetes in Youth Study.)

racial and ethnic groups.[2] These trends are elaborated below in this section. The increasing incidence of type 1 diabetes suggests a major environmental contribution, but the role of specific pathogenic factors remains largely unsettled. The distinction between type 1 and type 2 diabetes can become blurred in later life, and the true lifetime incidence of the condition is therefore unknown.

In Europe, the highest rates of childhood diabetes are found in Scandinavia, with an incidence for children from birth to 14 years of age ranging from 57 per 100,000 per year in Finland to 4 per 100,000 in Macedonia. In the United States, the overall annual incidence in youths is about 19 per 100,000. Prevalence rates are strikingly different among ethnic groups living in the same geographic region, probably because of genetic differences in susceptibility to the disease. Early-onset diabetes carries a higher familial risk, and affected fathers are more likely to transmit type 1 diabetes to their offspring than affected mothers are, with risks being 6 to 9% and 1 to 3%, respectively.

Given that the United States does not have a systematic health registry and that its population is multiethnic, previous estimates of the prevalence and incidence of type 1 diabetes have been based on extrapolations from limited cohorts. The SEARCH for Diabetes in Youth multicenter study (funded by the U.S. Centers for Disease Control and Prevention and the National Institutes of Health) examined diabetes among children and adolescents in the United States. During 2008–2009, an estimated 18,436 people younger than 20 years in the United States were newly diagnosed with type 1 diabetes and 5089 people younger than 20 years were newly diagnosed with type 2 diabetes. For those younger than 10 years, new cases of type 1 far outweighed type 2 (22.2 per 100,000 per year for type 1 diabetes vs. 0.8 per 100,000 for type 2 diabetes). Among youth aged 10 years or older, the rate of new cases of type 1 was about double that of type 2 (21.9 per 100,000 per year for type 1 diabetes vs. 11.0 per 100,000 for type 2 diabetes). Non-Hispanic white youth had the highest rate of new cases of type 1 diabetes in all age groups. Diabetes incidence rates by age and race/ethnicity are summarized in Figure 216-3.

Higher body mass index (BMI) is associated with younger age at diagnosis of type 1 diabetes, but this appears to be the case only in children with already compromised β-cell function. In addition, low birth weight may be a factor in accelerating the onset of type 1 diabetes, suggesting that the intrauterine environment may be an important determinant of age at onset for type 1 diabetes.

Pathobiology

In type 1 diabetes a complex interplay of genetic, environmental, and autoimmune factors selectively targets insulin-producing pancreatic islet β cells and ultimately destroys the β cells. The role of genetic factors in type 1 diabetes has long been appreciated, emphasized by familial clustering with other autoimmune endocrine disorders[3] and by concordance rates in identical twins of 30 to 40%. Because these concordance rates are not as high as in type 2 diabetes (i.e., >80%), environmental factors must clearly play a major role. Although the presence of an environmental trigger for type 1 diabetes is highly likely, even identical twins do not express identical T-cell receptor and immunoglobulin genes; as a result, total concordance might not be expected. Siblings who are

human leukocyte antigen (HLA) identical to the proband have a 12 to 15% risk for development of diabetes by the age of 20 years.

Although many of the genes linked to type 1 diabetes have yet to be identified, about 60 are known.[4] HLA genes, located on the short arm of chromosome 6, contribute about 50% of genetic susceptibility to type 1 diabetes.[5] Two HLA class II haplotypes, DR4-DQ8 and DR3-DQ2, are present in about 90% of children with type 1 diabetes. The genotype containing both haplotypes carries the highest risk of diabetes (about 5%) and is most commonly seen in early-onset disease. In contrast, the DR15-DQ6 haplotype is highly protective, being found in only 1% of children with type 1 diabetes in contrast to 20% in the general population. HLA susceptibility haplotypes are overrepresented in adult-onset type 1, but at lower frequency than in classic type 1 diabetes in youth. Other genes likely contribute to the genetic susceptibility to type 1 diabetes. These include the insulin gene (on chromosome 11) and a number of other loci that are associated with other autoimmune conditions, suggesting the existence of common pathways predisposing to loss of self-tolerance. Another gene, *IFIH1*, located on chromosome 2, encodes a protein involved in innate immunity and plays a role in recognition of the RNA genomes of certain viruses. It is suggested that high IFIH1 levels might provoke exaggerated antiviral immune responses that predispose to autoimmunity. Many other genes have also been implicated, underscoring the polygenic nature of this disease.

Historically, environmental causes of type 1 diabetes focused on viruses because of associations with seasonal pandemics of infections and rarely because of the isolation of a specific pathogen. Epidemics of mumps, rubella, and coxsackievirus infection have been associated with an increased frequency of type 1 diabetes. Moreover, specific and convincing rare examples of virus-induced diabetes have been reported. However, it is believed that virus-mediated β-cell damage is not responsible for the massive destruction of β cells but that it triggers an autoimmune response in genetically predisposed individuals. Thus viruses may contain molecules that resemble a β-cell protein, and viral infection could thus nullify self-tolerance and trigger autoimmune responses.

It has long been recognized that about 80% of patients with new-onset type 1 diabetes have antibodies directed against various islet cell proteins, including insulin, glutamic acid decarboxylase (GAD65 and GAD67), and the secretory granule protein islet cell antigen 512 (IA-2). These antibody biomarkers have been important tools for studying the potential for early identification and prevention of total β-cell destruction in individuals susceptible to type 1 diabetes. β-cell destruction is largely mediated by a variety of cytokines or by direct T-lymphocyte activity that causes apoptosis or cellular destruction, although evidence suggests that islet-directed antibodies may also play a role. Both animal models and human pathologic studies have established that islet-targeted inflammatory cell infiltrates (termed insulitis) that are composed of $CD8^+$ and $CD4^+$ T cells, macrophages, and B cells are linked to the onset of diabetes. Over time, the islets become completely devoid of β cells and inflammatory infiltrates; α, δ, and pancreatic polypeptide cells are left intact, thus illustrating the specificity of the autoimmune attack on β cells.

A critical role for T cells is suggested by studies involving pancreatic transplantation in identical twins. Monozygotic twins with diabetes who received kidney and pancreas grafts from their nondiabetic, genetically identical siblings required little or no therapeutic immunosuppression. However, these patients eventually experienced a resumption of insulitis, with the subsequent recurrence of diabetes. Evidence implicating T cells in diabetes autoimmunity also derives from clinical trials using immunosuppressive drugs. Drugs such as cyclosporine or antibodies directed against a component of the T-cell receptor (anti-CD3) or that alter antigen presentation by B cells (anti-CD20) slow the progression of recent-onset diabetes, but this effect is not sustained if immunosuppression is withdrawn.

Clinical Manifestations

It has been clearly established that type 1 diabetes has a long preclinical phase, best described in Figure 216-4. At the time of clinical diagnosis, about 10 to 20% of the original β-cell mass may still be functional. In most cases, overt hyperglycemia (and ketosis if it is present) may be precipitated by an unrelated medical illness or stress placed on an already-limited islet reserve, thus triggering the diagnostic clinical manifestations. Typically, symptomatic hyperglycemia, manifested by polyuria, polydipsia, weight loss, and fatigue, occurs abruptly in an otherwise healthy child or young adult. For a minority of patients, the initial presentation may be diabetic ketoacidosis (DKA), which can occur if there is a delay in recognizing the symptoms of diabetes. Whereas the disease has an increased incidence in the winter months, classically attributed to respiratory viral infections, this seasonal pattern may be the result of

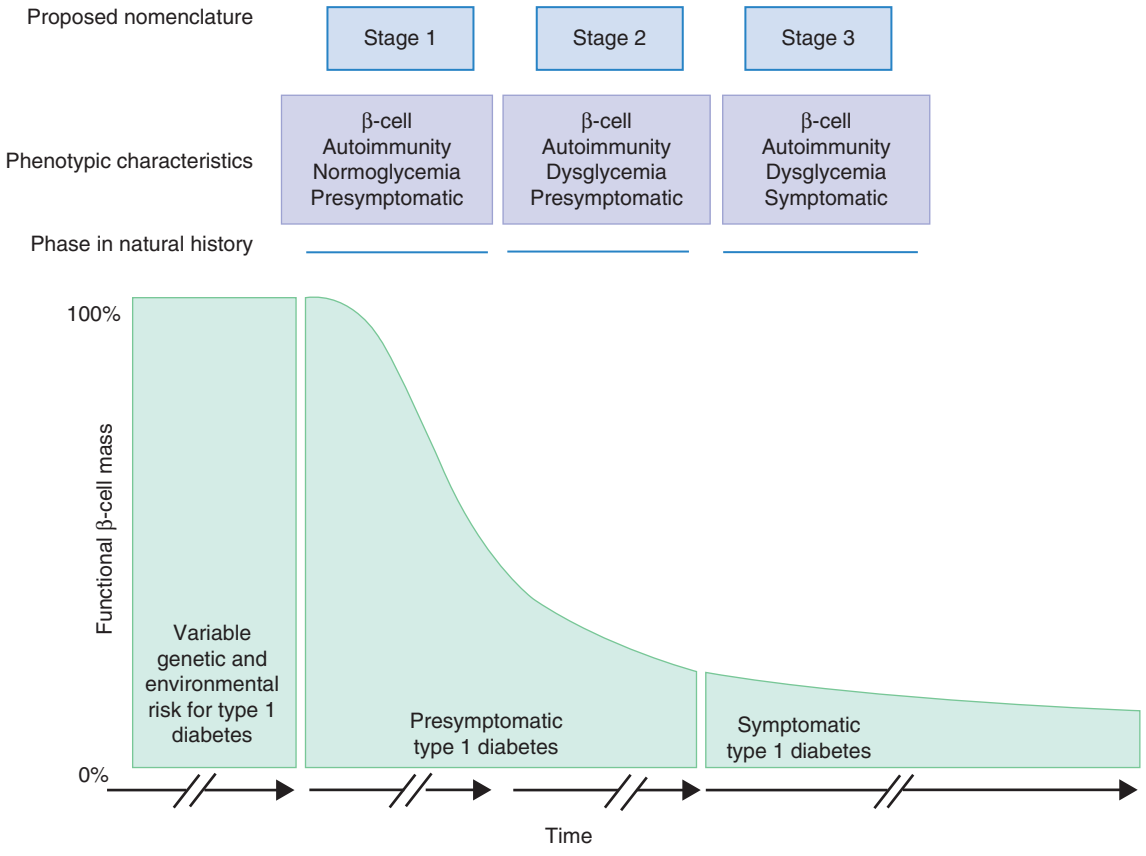

FIGURE 216-4. Summary of the sequence of events that lead to pancreatic β-cell loss and ultimately to the clinical evolution of type 1 diabetes. DKA = diabetic ketoacidosis. (From Insel RA, Dunne J, Atkinson MA, et al. Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association. *Diabetes Care.* Oct 2015;38[10]:1964-1974.)

illness-associated counter-regulatory hormones that drive hyperglycemia in individuals with already compromised β-cell function. Similarly, the coincidence of type 1 diabetes with puberty has been attributed to insulin resistance associated with increases in sex and growth hormone secretion.

The diagnosis of diabetes is made according to symptoms or glucose criteria (see Table 216-2). Rarely, measurement of anti–glutamic acid decarboxylase antibodies is performed, but the determination of type 1 etiology is generally made on clinical grounds. After initiation of insulin therapy and stabilization of plasma glucose levels, the patient may experience a period of weeks to months of relatively easily controlled hyperglycemia. This so-called honeymoon phase of type 1 diabetes results from amelioration of the underlying stress in the face of β-cell function that has not declined further, and reflects the severe but not total β-cell destruction with ongoing (albeit reduced) insulin secretion. Subsequently, the ongoing, progressive, decline in insulin production generally leads to undetectable levels after a few years. However, with highly sensitive C-peptide assays, low levels of insulin production have been detected in some patients with long-standing type 1 diabetes who demonstrate more stable glycemic control. In patients with onset of type 1 diabetes in adulthood, the clinical presentation may follow a more indolent course (termed latent autoimmune diabetes in adults), perhaps because β-cell mass declines at a slower pace. In fact, type 1 diabetes may be misdiagnosed as type 2 in many of these patients until the progression of insulin deficiency reveals the phenotype of permanent and complete insulin dependence.

TREATMENT

Rx

The key to successful treatment of type 1 diabetes is to achieve physiologic insulin replacement, that is, to replicate the normal and tightly regulated relationship between plasma glucose and insulin secretion. Although current technology can only mimic this normal physiology, substantial progress has been made to permit maintenance of relative euglycemia by many patients. Successful glucose management requires substantial commitment by the patient and health care practitioner.[6]

Insulin Therapy

All patients with type 1 diabetes require insulin treatment to maintain life. The approach to insulin replacement in type 1 diabetes requires consideration of both basal insulin requirements (insulin required to maintain homeostasis in the fasting state) and insulin required for the influx of nutrients that occurs with meals. A variety of insulin preparations is available, which differ by patterns of absorption after subcutaneous injection. Most currently used insulin preparations are analogues of human insulin that have been modified (usually by changing one or more amino acids) to alter pharmacokinetics to speed or to delay absorption (Table 216-5).

Patients with type 1 diabetes are treated with both a long-acting "basal" insulin and a shorter-acting "prandial" insulin at mealtime, by a multiple daily insulin injection regimen or a continuous subcutaneous insulin infusion pump. Typically, the daily insulin requirement for patients with type 1 diabetes is between 0.3 and 1.0 unit/kg/day, with half given as basal insulin and the remainder divided into pre-meal boluses. Prandial insulin doses are determined by meal carbohydrate content plus a "correction factor" if glucose is elevated before the meal. For example, a common approach is to use 1 unit for every 10 to 15 g of meal carbohydrate plus a correction factor of 1 unit to lower plasma glucose concentration by 20 to 50 mg/dL. However, insulin requirements are influenced by a number of factors (e.g., age, body size, insulin sensitivity) and vary substantially among patients; therefore these algorithms need to be individualized. A number of mobile phone applications and computer programs are available to assist patients with dose calculation. Critical to the success of physiologic insulin replacement is the need for the patient to monitor blood glucose concentration, generally several times a day (see later).

A continuous subcutaneous insulin infusion pump using a short-acting insulin analogue can be programmed to deliver both a basal infusion and a preprandial bolus. Most insulin pumps contain an insulin reservoir attached by thin flexible tubing to a very small catheter that is inserted subcutaneously by the patient and changed every 2 or 3 days to avoid local inflammation and fibrosis, which can interfere with insulin absorption. The basal insulin delivery rate can be programmed to vary throughout the day and may be especially useful to prevent hyperglycemia associated with the "dawn phenomenon" (rising blood glucose levels in the early morning hours, thought largely to be due to increased growth hormone secretion). Most insulin pumps can be programmed to calculate prandial insulin doses, based on pre-meal glucose level and meal carbohydrate content, which is entered by the patient. However, in the event of pump malfunction, metabolic decompensation, including DKA, can develop within several hours because there is no subcutaneous reservoir of long-acting insulin. Successful use of an insulin pump requires a motivated and educated patient plus the support of a specialized diabetes team, including a certified diabetes educator. Insulin pump therapy can be used successfully in children and adolescents and is associated with reduced rates of acute complications, including severe hypoglycemia and DKA, compared with insulin injection therapy.[7] When used appropriately, continuous subcutaneous insulin infusion provides patients with maximal lifestyle flexibility and the best chance to achieve near-normal blood glucose levels. More recently, hybrid closed-loop insulin delivery systems, in which a control algorithm autonomously and continually increases or decreases the subcutaneous delivery of basal insulin on the basis of real-time glucose levels recorded by a continuous glucose monitor (see below), have become available. These systems can improve glucose control and reduce hypoglycemia, compared with conventional insulin pump use.

Some patients who find adherence to a multiple injection or insulin pump regimen difficult can be treated with premixed "biphasic" insulin combinations, for example, a mixture of NPH and regular insulin given twice daily. This approach may be appropriate for patients with recent onset of type 1 diabetes who still maintain some endogenous insulin production. However, for most patients, this regimen is rarely optimal because it lacks flexibility and often increases the risk of hypoglycemia.

Diet and Lifestyle Treatment

In type 1 diabetes, the focus of dietary planning is on accurate estimation of meal carbohydrate content to allow appropriate prandial insulin dosing. This can be approached by promotion of "carbohydrate consistency" from meal to meal and the use of relatively fixed pre-meal insulin dosing. A more flexible approach is for the patient to learn "carbohydrate counting," which specifies an insulin dose per amount of carbohydrate in the meal. With either approach, patients need to monitor the nutrient content of their meals. Avoidance of concentrated sweets and other high-carbohydrate meals, including those with a high "glycemic index," tends to facilitate accurate insulin dosing and to minimize postprandial glycemic excursions. In contrast to type 2 diabetes, most patients with type 1 diabetes are not overweight or obese, and calorie restriction is neither required nor helpful. A variety of eating patterns are considered acceptable, and recommendations for a "heart healthy" diet (low in saturated fat and cholesterol) are the same as for the general population.

Glucose Self-Monitoring

Successful management of type 1 diabetes requires consistent self-monitoring of blood glucose concentration by the patient or caregiver several times a day. Small portable meters with disposable strips are easy to use and reasonably accurate in most ambulatory care settings. Frequent testing (i.e., before meals and at bedtime) allows appropriate prandial insulin dosing and correction of unexpected hyperglycemia as well as detection or confirmation of hypoglycemia. Most current meters store a large number of readings, which can be downloaded to a computer for analysis by the patient and health care team. Subcutaneous glucose monitors that provide continuous reading of interstitial glucose levels are available and are most commonly used in conjunction with an insulin pump. These monitors are most useful to determine glucose patterns and some can be programmed to sound an alarm when the glucose level exceeds a preset range or rate of change. The accuracy of continuous glucose monitoring (CGM) technology has improved substantially and may allow it to be used in place of conventional blood glucose measurement for immediate decision making and use in a closed loop system with an insulin pump. Evidence suggests that use of CGM, compared with usual care, can improve glycemic control for many patients, including those using conventional insulin injection therapy.

Patients with type 1 diabetes should be also instructed to test urine ketones (with a reagent strip) in situations in which blood glucose concentration is unexpectedly and persistently elevated, especially if it is accompanied by

TABLE 216-5 INSULIN PREPARATIONS

TYPE OF INSULIN	ONSET OF ACTION	PEAK EFFECT	DURATION OF ACTION
BASAL INSULIN			
Glargine	Approximately 2 hours	None	Approximately 24 hours
Detemir	Approximately 2 hours	3-9 hours	6-24 hours
Degludec	Approximately 2 hours	None	Approximately 40 hours
NPH/NPL	Approximately 2 hours	6-12 hours	14-24 hours
PRANDIAL INSULIN			
Lispro, aspart, glulisine	5-15 minutes	45-75 minutes	2-4 hours
Regular	Approximately 30 minutes	2-4 hours	5-8 hours

NPH = neutral protamine Hagedorn; NPL = neutral protamine lispro.

symptoms suggestive of DKA (see section on diabetic ketoacidosis under hyperglycemic states in acute metabolic complications of diabetes). Small or trace amounts of urinary ketones are not cause for concern, but moderate or large amounts may indicate the onset of DKA and should prompt the patient to seek urgent medical attention.

Whole Pancreas and Islet Cell Transplantation

The ultimate goal of a "cure" of type 1 diabetes could most likely be achieved by successful transplantation of insulin-producing β cells. Whole pancreas transplantation has been performed for almost three decades, with 5-year graft survival rates of about 70%. However, the surgery is complicated, and lifelong immunosuppression is required, as with any organ transplant. For these reasons, pancreas transplantation is generally reserved for patients who already have or are concurrently receiving a kidney transplant. In the absence of indications for kidney transplantation, pancreas-alone transplantation may be considered for patients who have a history of frequent, acute and severe metabolic complications (especially severe hypoglycemia) or severe and incapacitating psychosocial problems related to insulin therapy. Pancreatic islet cell transplants hold significant potential advantages over whole-gland transplants. However, at this time, islet cell transplantation is an experimental procedure, also requiring systemic immunosuppression, and is performed only within the setting of controlled research studies.

Prevention of Type 1 Diabetes

Given that type 1 diabetes is an immunologically mediated disease, it has long been supposed that immune intervention should alter its natural history and perhaps even prevent it altogether.[8] Furthermore, the significant heritability of type 1 diabetes suggests that treatment could target only susceptible individuals, and the existence of known biomarkers (antibodies that reflect disease activity as well as levels of insulin or C-peptide that reflect islet function) also lends credence to experimental immunologic treatments. Unfortunately, however, the major challenge for most immunologic interventions has been their lack of specificity for immune-mediated insulitis or the risks of spillover immune suppression in otherwise healthy persons. Given the experimental nature of all the tested therapies, we provide only a brief overview here.

Prevention of type 1 diabetes can theoretically be undertaken at three stages: (1) in susceptible individuals before there is evidence of immune attack against islet cells (primary prevention); (2) in nondiabetic people who already have evidence of immune activation (antibodies, insulin defects) to prevent progression to actual diabetes (secondary prevention); and (3) in newly diagnosed patients in whom the goal is to slow the β-cell destructive process (tertiary prevention).

Avoidance of putative environmental triggers of islet autoimmunity (e.g., cow's milk) is one approach, and dietary supplementation with nutrients that may diminish islet autoimmunity (e.g., omega-3 fatty acids or vitamin D) has been attempted. Despite promising results of a pilot study, a large trial of primary prevention by removal of cow's milk from the infant diet failed to reduce incident diabetes over 11 years of follow-up. Secondary prevention trials have also been undertaken with oral, inhaled, or injected insulin and with nicotinamide, but the results have been disappointing. There are secondary prevention studies with teplizumab (an FcR-nonbinding anti-CD32 monoclonal antibody) and with abatacept (a costimulation modulator) underway. Several tertiary prevention studies (i.e., after the diagnosis of diabetes) have been published. Nonspecific immune interventions, such as cyclosporine, demonstrate that immunotherapy can indeed rescue β cells from ongoing destruction, but it is not an acceptable therapeutic alternative given that it preserves β-cell function only transiently and carries heightened risks of adverse effects, such as nephropathy. Anti-CD3 antibodies currently appear more promising and are being evaluated in clinical trials.

Prognosis

Substantial progress has been made in recent decades in improving the prognosis for patients affected by type 1 diabetes. This is largely due to adoption of more intensive glucose control and more effective nonglycemic treatment of early stages of renal disease and retinopathy. Data from long-term follow-up of the intensively treated DCCT cohort showed that after 30 years' duration of diabetes, rates of serious diabetes complications were substantially lower than in historical controls, and less than 1% became blind, required renal replacement, or had an amputation due to diabetes. In Sweden from 1998 through 2014, mortality and the incidence of cardiovascular complications declined substantially among type 1 diabetic persons.[9,10] In the absence of renal disease, life expectancy for type 1 patients in the United States is comparable to that of the general population. However, the mortality rate of all type 1 diabetic patients from age 35 onward is about twice as high as in non-diabetics even if the $HgbA_{1c}$ level is 6.9% or lower and becomes progressively higher for $HgbA_{1c}$ levels above 7.9%. Analysis of nationally representative hospitalization and registry data has shown large reductions in the incidence of a broad spectrum of diabetes-related complications between 1985 and 2015 in the U.S. population of adults with diabetes[11]; however, despite the substantial decline in the rates of diabetes-related complications in the past two decades, a large burden of disease persists because of the continued increase in the prevalence of diabetes.

TYPE 2 DIABETES

Epidemiology

Type 2 diabetes is one of the most common chronic diseases, affecting more than 30 million people in the United States and an estimated 366 million worldwide.[12] The prevalence of type 2 diabetes has been increasing in the United States, from approximately 3% of the population in 1995 to more than 9% in 2015.[13,14] This increase is in part due to demographic shifts (i.e., the aging of the population), but incidence rates are also increasing and parallel the rise of overweight and obesity as well as increasingly sedentary lifestyles. A similar pattern is observed globally, with projections of 550 million (approximately half undiagnosed) to be affected by 2030. Although type 2 diabetes is being increasingly recognized in obese adolescents and young adults, older age remains a major risk factor for type 2 diabetes. More than one quarter of adults age 65 years and older have diabetes, and another 50% have glucose or HbA_{1c} levels in the impaired or pre-diabetic range. Type 2 diabetes in the United States is more common among some racial and ethnic groups, with prevalence rates highest among non-Hispanic blacks (18%), Hispanics (16%), and American Indians (16%) and lowest among non-Hispanic whites (9%). Individuals from the Indian subcontinent (i.e., India, Pakistan, Bangladesh) and the Pacific Islands (e.g., Hawaii, Nauru, Samoa) also have high rates of type 2 diabetes. In general, men and women have about equal prevalence of type 2 diabetes.

Pathobiology

Type 2 diabetes is characterized by variable defects in both insulin secretion and insulin action. The underlying metabolic phenotype of type 2 diabetes is distinctly heterogeneous among individuals with the disease; some have a more pronounced defect in insulin secretion, and others have greater resistance to insulin action. The metabolic profile also varies within a given patient over time, as insulin secretion progressively declines with longer duration of disease. Although heterogeneous, type 2 diabetes is characterized in all cases by inadequate insulin secretion for the prevailing glucose level and degree of insulin sensitivity.

IMPAIRED INSULIN SECRETION

The relative insulin deficiency characteristic of type 2 diabetes appears to be a consequence of both functional (i.e., reduced responsiveness to secretagogues) and quantitative (i.e., reduction in β-cell mass) factors. Insulin secretory capacity is difficult to directly measure in humans, but reductions of β-cell mass up to 60% are estimated to occur in type 2 diabetes. However, this alone is insufficient to explain insulin deficiency in type 2 diabetes, as evidenced by the observation that 50% surgical pancreatectomy does not lead to hyperglycemia in otherwise healthy individuals. Classic studies in diabetic patients have demonstrated failure of insulin secretion in response to glucose but a normal response to the amino acid arginine, providing further evidence for the presence of a functional defect specific to glucose sensing. Abnormalities in the usual pulsatile and oscillatory patterns of insulin secretion and inefficient insulin biosynthesis have also been demonstrated in type 2 diabetes. For example, abnormal peptide processing results in increased secretion of intact proinsulin, which serves as a useful biomarker of future diabetes risk. Increased accumulation of amyloid also occurs within diabetic islets and may contribute to impaired secretory function. Ultimately, the β-cell defects in type 2 diabetes appear to be multifactorial, in part genetically determined (see later) but also influenced by environmental exposure, for example, to high levels of circulating glucose (glucotoxicity) and lipids (lipotoxicity). In addition, the β-cell defects are not static but worsen with increasing duration of diabetes.

IMPAIRED INSULIN ACTION (INSULIN RESISTANCE)

Resistance to the metabolic effects of insulin is also a characteristic although variable feature of type 2 diabetes. Hyperinsulinemia, thought to be a

compensatory response to impaired insulin action, can be demonstrated in patients with pre-diabetes and in many patients with established type 2 diabetes, particularly early in its course. More precise techniques to measure insulin action (e.g., the euglycemic hyperinsulinemic clamp) have demonstrated resistance to insulin action primarily in peripheral tissues (reduced capacity to stimulate glucose uptake in muscle and fat) but also in the liver (reduced capacity of insulin to suppress hepatic glucose production). Insulin resistance is closely associated with obesity (see later) but also has genetic determinants, reflected by the observation that some obese patients do not have severe insulin resistance. Insulin resistance frequently occurs as part of a constellation of features, termed the *metabolic syndrome*, which include hypertension, abdominal obesity, dyslipidemia, glucose intolerance, and increased cardiovascular risk. Insulin resistance is also a common feature of the polycystic ovary syndrome.

There are multiple molecular mechanisms that can lead to resistance to physiologic insulin action, including pre-receptor defects (e.g., an abnormal insulin molecule) and abnormal insulin receptors (e.g., due to gene mutations). However, common forms of insulin resistance that occur in association with type 2 diabetes are generally due to post-receptor defects, that is, abnormalities in intracellular signaling. In insulin target tissues, signaling through the phosphatidylinositol 3-kinase pathway is responsible for translocation of the glucose transporter GLUT4, which is necessary for uptake of glucose into the cell. Several defects in this pathway have been described in humans with insulin resistance, including abnormalities in insulin receptor substrate 1 and protein kinase B/Akt2. Some specific gene mutations associated with insulin resistance have been identified, but insulin resistance may also be acquired as a consequence of obesity (see later), increases in circulating free fatty acids, certain medications (e.g., glucocorticoids, niacin), and inflammatory states.

Evidence from natural history and genetic association studies (see later) indicates that defects in either insulin action or insulin secretion can remain clinically silent. For example, insulin resistance can induce compensatory hyperinsulinemia, which early in the course of the disease is sufficient to maintain euglycemia. However, in individuals with inherited or acquired defects in β-cell function, this compensation ultimately fails and hyperglycemia ensues. Viewed another way, a subclinical β-cell defect may remain silent in the setting of normal insulin sensitivity but be manifested as hyperglycemia when acquired insulin resistance develops because of weight gain, aging, or some other factor. A unifying theory that explains the coexistence of defects in both insulin action and insulin secretion is appealing but so far elusive.

GENETICS

The evidence for familial aggregation of type 2 diabetes is substantial and supports the presence of an important genetic influence. An individual with one parent with type 2 diabetes has a lifetime risk for development of type 2 diabetes of approximately 40%, with risk increasing to approximately 70% if both parents are affected. Further, the concordance rate among monozygotic twins is as high as 70%. The greater risk of type 2 diabetes among certain racial and ethnic groups also supports an important genetic component. The overall heritability of type 2 diabetes is estimated to be between 25 and 50%, although the specific gene or genes ultimately responsible for common forms of type 2 diabetes have not been established.[15]

Single-Gene Mutations Linked to Type 2 Diabetes Phenotype

A number of syndromes, termed *maturity-onset diabetes of youth* (MODY), characterized by impaired β-cell function have been recognized and linked to specific single-gene mutations. The phenotypes vary with the mutation but generally include early onset of relatively mild hyperglycemia in nonobese children or young adults and an autosomal dominant pattern of inheritance. Although not common (representing 1 to 3% of diabetes cases worldwide), their discovery has provided insight into the role of β-cell function in the more common forms of type 2 diabetes. MODY 2 is associated with a mutation of glucokinase, which acts as a glucose sensor within the β cell. In this case, higher levels of glucose are required to stimulate release of insulin from the β cell. MODY 3 is due to a mutation of the gene for hepatic nuclear factor 1α, which is involved in early pancreatic development and in the regulation of insulin gene expression. Other MODY forms (1, 4, 5, 6) are much less common, having been described in only a few families (Table 216-6).

Other examples of single-gene mutations associated with specific diabetes syndromes include activating mutations of *KCNJ11* (encoding a portion of the β-cell sulfonylurea receptor), which causes severe neonatal diabetes, and *WFS1*, which encodes a protein that is defective in Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness).

TABLE 216-6 SINGLE-GENE MUTATIONS RESPONSIBLE FOR THE MORE COMMON FORMS OF MATURITY-ONSET DIABETES OF YOUTH (MODY)

	MUTATION	METABOLIC DEFECT	CLINICAL PHENOTYPE
MODY 2	Glucokinase	Decreased β-cell sensitivity to glucose	Mild nonprogressive hyperglycemia, may not require pharmacologic treatment; diabetes complications rare
MODY 3	Hepatic nuclear factor 1α	Abnormal regulation of β-cell gene transcription	Mild hyperglycemia, may be progressive; renal glycosuria; increased sensitivity to sulfonylurea drugs; susceptibility to microvascular complications

Polygenic, Common Type 2 Diabetes

Common forms of type 2 diabetes are likely polygenic and multifactorial and represent a complex interaction between genes and environment. In the past several years, more than 100 genetic risk loci for common forms of type 2 diabetes have been identified by genome-wide association studies, but collectively these explain less than 15% of the heritability of the disorder. Outside of rare variants that are unique to specific groups, the gene with the strongest effect size to date (odds ratio for diabetes, 1.4) is *TCF7L2*, which is associated with reduced insulin secretion, as are the majority of other recognized gene variants. Others include a β-cell zinc transporter (ZnT-8; odds ratio, 1.15), the sulfonylurea receptor (*KCNJ11*; odds ratio, 1.1), and melatonin receptor 1B (*MTNR1B*; odds ratio, 1.10). A smaller number of gene variants associated with insulin resistance have been identified and include genes encoding peroxisome proliferator-activated receptor γ (odds ratio, 1.20) and insulin receptor substrate 1 (odds ratio, 1.10). Sequence variants in *SLC16A11*, a gene involved in intracellular lipid metabolism, were discovered to be a relatively common risk allele (odds ratio, 1.29) in Mexican populations. Current knowledge about genetic variants associated with type 2 diabetes risk is not useful for clinical disease prediction, offering no advantage to simple clinical tools based on traditional risk factors.

There is emerging evidence that epigenetic changes may play an important role in development of type 2 diabetes. Epidemiologic studies suggest that "metabolic programming" may occur in utero, with both fetal starvation and fetal overnutrition predisposing to diabetes in adult life. One example comes from experience with the Pima Indians, who have an extremely high prevalence of type 2 diabetes. Children born to mothers who were diabetic during their pregnancy had higher rates of adult diabetes than did children born to the same mothers before they became diabetic, suggesting that intrauterine exposure can have long-lasting metabolic effects. Studies of DNA methylation in animal models support this hypothesis, although human epigenome-wide studies are just now being conducted. Conversely, maternal undernutrition is associated with diabetes in offspring. Low birth weight has been linked to predisposition to cardiovascular disease and diabetes in adulthood. According to the widely cited Barker hypothesis, nutrient deficiency in utero (e.g., due to maternal starvation or placental insufficiency) impairs development of the endocrine pancreas, leading to inadequate insulin production later in life.[16] The available data suggest that maternal nutrition may play an important role in metabolic programming, resulting in increased diabetes susceptibility in adulthood.

OBESITY

The presence of overweight or obesity (Chapter 207) substantially increases the risk for type 2 diabetes and likely accounts for the dramatic increase in diabetes prevalence during the past several decades. In fact, the presence of overweight or obesity is the single most important clinical predictor of type 2 diabetes, particularly for young or middle-aged individuals. The relationship between BMI and type 2 diabetes is linear, and increased risk can be observed even within the BMI range defined as normal (<25 kg/m^2). Related factors, such as sedentary lifestyle and diet (increased consumption of foods with high glycemic load, increased *trans* and saturated fat), may also contribute to diabetes risk, independent of BMI. Distribution of body fat also plays an important role, with visceral adiposity (as assessed by waist circumference or waist-to-hip ratio) being a particularly strong diabetes risk factor in Asian

populations, who tend to develop type 2 diabetes at a lower BMI than some other racial or ethnic groups do. Ectopic accumulation of adipose tissue in the liver, often manifested as nonalcoholic fatty liver disease, is also strongly associated with increased diabetes risk.

The increase in adipose tissue mass impairs insulin action by a number of proposed mechanisms, including alterations in fatty acid metabolism, accumulation of triglycerides in the liver, and low-grade systemic inflammation. Adipose tissue macrophages produce proinflammatory cytokines, including tumor necrosis factor–α and interleukin-6, which can interfere with insulin signaling. Obesity is also associated with reduced levels of the fat-derived peptide adiponectin, which exhibits both anti-inflammatory and insulin-sensitizing properties. The increase of circulating free fatty acids that is characteristic of obese states can interfere with insulin action in skeletal muscle and liver, and increased intramyocellular lipid is also associated with insulin resistance. Further, increased lipid accumulation in pancreatic islets may lead to impaired insulin secretion. Interestingly, some obese individuals have apparently normal insulin sensitivity and glucose metabolism, sometimes referred to as the obesity paradox. The mechanisms that may protect someone from the diabetogenic effects of excess adiposity are not known, but intact cardiorespiratory fitness may play a role.

Clinical Manifestations

TYPICAL TYPE 2 DIABETES

The classic hyperglycemic symptoms of polyuria, polydipsia, and weight loss occur when the renal threshold for glucose reabsorption (about 180 mg/dL) is exceeded and glycosuria with osmotic diuresis occurs. Therefore patients may have a plasma glucose concentration that is elevated but below this threshold, for years if not for decades, before specific symptoms appear. In the current era many patients are found to have diabetes during routine screening or in the course of investigation for another disorder (typically CVD). The initial presentation for some patients may be severe decompensated hyperglycemia, with profound dehydration, electrolyte imbalance, and plasma glucose levels of 400 mg/dL or higher, with the most striking examples being hyperosmolar hyperglycemic state (HHS) and DKA (see corresponding sections later).

A key feature of type 2 diabetes is that the metabolic defects are not static but tend to worsen over time. A patient early in the course of type 2 diabetes may maintain acceptable glucose control with simple dietary modification and modest weight loss. For many patients, these measures alone fail over time, and combinations of oral medications and often insulin therapy become necessary to control blood glucose levels.

Although the defining clinical feature of type 2 diabetes is hyperglycemia, it is actually the vascular complications of the disorder that cause the greatest morbidity and mortality. For a minority of patients, the initial clinical presentation of diabetes may be the presence of diabetic microvascular complications (retinopathy, neuropathy, nephropathy), which usually indicates many years of unrecognized hyperglycemia. More typical is the insidious onset of symptomatic microvascular complications after many years of diabetes, especially if it is poorly controlled.

ATYPICAL DIABETES

DKA may be the initial clinical presentation for a minority of patients with type 2 diabetes, who subsequently recover β-cell function and do not require insulin treatment. This entity, referred to as ketosis-prone type 2 or Flatbush diabetes (named for the New York City neighborhood where it was first described), appears to be more common among African Americans and some other ethnic minorities. These patients typically lack markers of β-cell autoimmunity and have a strong family history of type 2 diabetes. Once the initial episode of DKA is treated and glucose levels stabilize, patients may have near-normoglycemic remissions lasting many years. The pathogenesis of this form of diabetes is not clear, but a unique β-cell predisposition to glucose desensitization ("glucose toxicity") has been proposed.

GESTATIONAL DIABETES

Diabetes that appears for the first time during pregnancy and typically regresses after delivery is termed *gestational diabetes* (Chapter 226). Women who develop gestational diabetes usually have risk factors including overweight or obesity, older age (>30 years), and a family history of type 2 diabetes. The majority will develop permanent type 2 diabetes during their lifetime. Hormonal changes (increases in placental lactogen, estrogen, progesterone) induce insulin resistance during pregnancy and may uncover latent β-cell defects in predisposed women. Babies born to mothers with diabetes mellitus are at risk for a number of adverse outcomes, especially macrosomia but also preterm birth, neonatal hypoglycemia, and hyperbilirubinemia. Routine screening, with an oral glucose tolerance test, of all pregnant women at 24 to 28 weeks of gestation is currently recommended. Because glucose levels tend to be lower than in the nonpregnant state, separate criteria have been developed for the diagnosis of diabetes in pregnancy. These include the presence of any of the following: fasting glucose concentration of 92 mg/dL or higher; glucose concentration of 180 mg/dL or higher at 1 hour or 153 mg/dL or higher at 2 hours after a 75-g oral glucose load. Aggressive glycemic control has been shown to reduce adverse pregnancy outcomes, including macrosomia and traumatic delivery, although its effects on long-term outcomes in offspring have not been established. Medical nutrition therapy is recommended for all women with gestational diabetes, with emphasis on moderate carbohydrate intake and avoidance of excessive weight gain. If diet modification is inadequate to maintain euglycemia, insulin has historically been considered first-line pharmacologic treatment for gestational diabetes. Oral diabetic medications, including glyburide and metformin, are increasingly being used to treat gestational diabetes, although long-term safety has not been established and they are not approved for this indication by the U.S. Food and Drug Administration. A multicenter noninferiority trial in women with gestational diabetes has failed to show that the use of glyburide compared with subcutaneous insulin does not result in a higher frequency of perinatal complications.■ After delivery, women with gestational diabetes should continue to be observed for the development of type 2 diabetes.

TREATMENT

Rx

Effective treatment of type 2 diabetes is uniquely challenging because it encompasses management of lifestyle factors (including diet, exercise, and weight control), use of multiple oral or injectable medications, self-monitoring of blood glucose concentration, and surveillance and treatment for acute and chronic diabetic complications. The active participation of the patient in this complex program is critical for successful diabetes management, and many patients benefit from participation in a program of diabetes self-management education.

Goals of Therapy Including Glucose Targets

The primary goals of diabetes management are to prevent symptomatic hyperglycemia and hypoglycemia and to prevent the vascular complications associated with diabetes (see later section on chronic vascular complications). Intensive glycemic control (near-normoglycemia) has been shown to reduce microvascular and neuropathic complications of diabetes but not CVD or mortality.■■ The current consensus view is that lowering of the HbA_{1c} level to 7% or below is an appropriate goal for most patients with diabetes. More stringent glycemic control (HbA_{1c} level close to the normal range) may be appropriate for some individuals (e.g., young patients with short duration of disease) if it can be achieved without excessive hypoglycemia. Conversely, less stringent goals may be suitable for patients with established vasculopathy, significant comorbidities, or reduced life expectancy. Generally accepted targets for fasting and postprandial glucose levels are 80 to 130 mg/dL and less than 180 mg/dL, respectively. Glycemic targets during pregnancy are different, in part because plasma glucose levels normally are lower during pregnancy and because of the risk of adverse fetal outcomes with even modest hyperglycemia (Table 216-7).

Diet and Lifestyle Management

Dietary recommendations for patients with type 2 diabetes have varied over the years and in the past included strict avoidance of sugars and the use of specific diet plans (e.g., "exchange systems") that provided prescribed amounts of carbohydrate, fat, and protein. Current approaches for most patients focus on calorie restriction to achieve and to maintain modest (approximately 5 to

TABLE 216-7 RECOMMENDED GLYCEMIC TARGETS FOR ADULTS WITH DIABETES

	PREPRANDIAL GLUCOSE LEVEL	POSTPRANDIAL GLUCOSE LEVEL	HbA_{1c}
Nonpregnant adults	80-130 mg/dL	<180 mg/dL	<7%
Gestational diabetes	≤95 mg/dL	<140 mg/dL (1 hour after meal) or <120 mg/dL (2 hours after meal)	—
Pre–gestational diabetes	<95 mg/dL	<140 mg/dL (1 hour after meal) or <120 mg/dL (2 hours after meal)	6-6.5%

Modified from American Diabetes Association standards of medical care in diabetes—2018. *Diabetes Care.* 2018;41(Suppl 1):S55-S64.

10% of body weight) weight loss, moderate carbohydrate intake, and avoidance of concentrated sweets and foods high in saturated fats and cholesterol. An optimal macronutrient distribution for patients with type 2 diabetes has not been established, and individualization of nutrition plans, depending on such factors as renal function, weight status, and the patient's preference, is recommended. Evidence suggests that a low-fat, low-carbohydrate (Atkins-type) diet and a Mediterranean-type diet can each be effective in promoting weight loss and improving glucose control in patients with diabetes. Moderate alcohol consumption is not prohibited, with the proper consideration of calorie intake (7 kcal/g) and hypoglycemia risk if alcohol is consumed without food, particularly in insulin-treated patients. Referral to a registered dietitian for medical nutrition therapy should be considered for patients newly diagnosed with type 2 diabetes and those who are not achieving glycemic or weight targets.

Regular exercise is an important but often overlooked component of diabetes management. Both aerobic exercise and resistance training can improve blood glucose control, even in the absence of significant weight change. Current recommendations are for a minimum of 150 minutes per week of moderate-intensity physical activity, such as brisk walking, biking, or swimming, and muscle-strengthening exercises two or three times per week. Assessment of cardiovascular status before beginning of an exercise program should be considered for selected patients, but routine screening (e.g., with an exercise stress test) of asymptomatic patients is not recommended. The presence of some diabetic complications may require restriction of certain activities. For example, in patients with proliferative retinopathy, vigorous aerobic or resistance exercise could precipitate retinal hemorrhage or detachment. The presence of significant sensory loss due to peripheral neuropathy can increase the risk of foot injury, including skin ulceration and Charcot joint destruction. Use of proper footwear and careful foot inspection are recommended, and avoidance of weight-bearing exercise may be required for high-risk patients. Finally, exercise-induced hypoglycemia can occur in patients treated with insulin or some secretagogues (i.e., sulfonylureas) and may require adjustment of the medication regimen or added carbohydrate before exercise.

Bariatric Surgery

Weight loss is considered the cornerstone for treatment of patients with type 2 diabetes, the majority of whom are overweight or obese. It has been clearly shown to improve glucose control. As expected, diabetic patients who undergo bariatric (weight reduction) surgery (Chapter 207) also show improvement in glucose control, which in some cases is dramatic. Improvements in glycemia often occur almost immediately after surgery, before significant weight loss has occurred, and appear to be related to changes in gut hormones (including GLP-1 and GIP) or bile acid metabolism. Many patients are able to discontinue diabetes medications, and diabetes remission rates above 50% have been reported. Among obese patients with uncontrolled type 2 diabetes, 3 years of intensive medical therapy plus bariatric surgery was reported to result in glycemic control in significantly more patients than did medical therapy alone; bodyweight, use of glucose-lowering medications, and quality of life also showed more favorable results at 5 years in the surgical groups.

Pharmacologic Therapy

Although weight control and nutrition form the foundation of effective management, most patients with type 2 diabetes will require use of pharmacologic agents, often multiple, to maintain recommended levels of glycemic control. During the last two decades, several new classes of drugs, targeting different metabolic pathways, have become available for treatment of type 2 diabetes. However, some of the most effective drugs are the oldest, and the long-term safety profile of newer agents remains to be established. Medications can be broadly categorized as those that enhance insulin availability (insulin and insulin secretagogues), those that enhance insulin action, or a miscellaneous group with other targets. Insulin therapy is also covered later and in the section on type 1 diabetes.

Insulin Sensitizers

Metformin

The biguanide drug metformin is the most widely used antidiabetic medication and is considered preferred initial therapy for patients with type 2 diabetes. The pleiotropic effects of metformin are thought to be mediated primarily through inhibition of mitochondrial complex 1 (i.e., effects on mitochondrial oxidative phosphorylation and cellular energy charge) and, in part, through regulation of the activity of 5′-adenosine monophosphate–activated protein kinase and the mammalian target of rapamycin. Metformin lowers glucose levels primarily through suppression of hepatic glucose production, but it also may enhance insulin sensitivity (improved insulin-mediated glucose uptake) and limit intestinal glucose absorption. Modest and sustained weight loss (about 2 to 4 kg) is common with metformin. Metformin is used orally twice a day, and extended-release forms are available for once-daily dosing. Hypoglycemia occurs rarely if at all with metformin monotherapy. The most common adverse effect is gastrointestinal intolerance (dyspepsia, diarrhea), which can be minimized by slow upward dose titration. Vitamin B_{12} malabsorption, leading to clinical B_{12} deficiency, has also been reported. The occurrence of lactic acidosis is the most serious although rare adverse effect, which occurs almost exclusively in patients with renal insufficiency and another precipitating factor, such as sepsis or shock. Renal function should be monitored periodically; metformin must be used with caution in those with an estimated glomerular filtration rate (GFR) of 45 mL/minute or lower and should be discontinued for an estimated GFR of 30 mL/minute or lower. Unique among available antidiabetic therapies, metformin was shown to reduce cardiovascular and all-cause mortality in the U.K. Prospective Diabetes Study (UKPDS), which adds to its appeal as a first-line agent. Metformin has also been used for diabetes prevention and for treatment of polycystic ovary syndrome.

Thiazolidinediones

The thiazolidinediones, which include rosiglitazone and pioglitazone, improve insulin-mediated glucose uptake and reduce hepatic glucose production. They bind to a nuclear receptor, peroxisome proliferator-activated receptor γ, and thus regulate the transcription of a variety of genes involved in carbohydrate and lipid metabolism. Thiazolidinedione therapy has pronounced effects on adipose tissue, reducing lipolysis, increasing fat mass, and causing redistribution of fat away from visceral to subcutaneous depots. Increases in circulating adiponectin, an adipokine with insulin-sensitizing and anti-inflammatory properties, may also play a role in the glucose-lowering effect of these drugs. Thiazolidinediones are given orally in once-a-day dosing. Common adverse effects include weight gain and fluid retention, including precipitation or worsening of congestive heart failure. Also reported have been an increase in fractures in postmenopausal women and increased risk of bladder cancer. The potential cardiovascular toxicity of rosiglitazone remains controversial, and its use has been restricted in many countries; these effects have not been observed for pioglitazone.

Insulin Secretagogues

Sulfonylureas

The sulfonylurea class of insulin secretagogues is among the oldest available oral antidiabetes drugs. Sulfonylureas currently in common use include glipizide, glyburide, and glimepiride; older sulfonylureas (chlorpropamide, tolbutamide) are still sometimes used outside of the United States. Their mechanism of action is to bind to the ATP-sensitive potassium channel in the β-cell membrane (at a site termed the *sulfonylurea receptor*), resulting in membrane depolarization and, ultimately, release of insulin from preformed secretory granules. Therefore the presence of a sufficient mass of intact β cells is required for efficacy of these drugs. They can be used as monotherapy or in combination with other drugs. The major adverse effect of sulfonylureas is their potential to cause hypoglycemia because insulin secretion occurs regardless of ambient plasma glucose. Modest weight gain is also common. Results of a study conducted in the 1970s (University Group Diabetes Program) suggested that sulfonylurea drugs may increase the risk of cardiovascular events and mortality. These findings were not confirmed in other trials, but the issue remains controversial. Despite this, sulfonylureas are among the most widely used antidiabetic medications.

Glinides

Repaglinide and nateglinide are chemically distinct non-sulfonylurea insulin secretagogues that also bind to the ATP-sensitive potassium channel in the β-cell membrane. Their onset and duration of action are much shorter than those of sulfonylureas, and the frequency of fasting hypoglycemia may be less. They are administered orally before each meal, making them somewhat less convenient than medications with a single daily dose but potentially providing an advantage for patients with inconsistent meal timing or content.

Incretin-Based Therapies/GLP-1 Agonists

Exenatide, liraglutide, semaglutide, dulaglutide, and lixisenatide are analogs of the endogenous incretin hormone GLP-1 and stimulate insulin secretion by binding to GLP-1 receptors on β cells. These drugs augment glucose-stimulated insulin secretion and thus have less potential to cause hypoglycemia than sulfonylureas and glinides do. They also suppress hepatic glucose production (by reduction of glucagon secretion), delay gastric emptying, and suppress appetite, resulting in modest weight loss for many patients. GLP-1 agonists are given by injection once or twice a day, and weekly long-acting formulations are also available. Major adverse effects include gastrointestinal intolerance (nausea and vomiting), which can be minimized by initiation with a low dose and gradual titration. In combination with basal insulin treatment, these agents can improve glycemic control without increasing hypoglycemia and often induce significant weight loss. Liraglutide also reduces all-cause mortality by about 15%, as well as reducing the risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Liraglutide, added to usual care, also resulted in lower rates of the development and progression of diabetic kidney disease than placebo. Similarly, weekly semaglutide (0.5 or 1.0 mg) significantly reduces the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in type 2 diabetes patients who are at high cardiovascular risk. Improvement in renal outcomes has also been reported for liraglutide and semaglutide. An increased risk of acute pancreatitis has been reported with GLP-1 agonists (and DPP-4 inhibitors; see later), but the magnitude of the risk is uncertain and requires additional research. An increase in C-cell hyperplasia and medullary thyroid cancer was found in laboratory animals, although the relevance of this to humans is unclear.

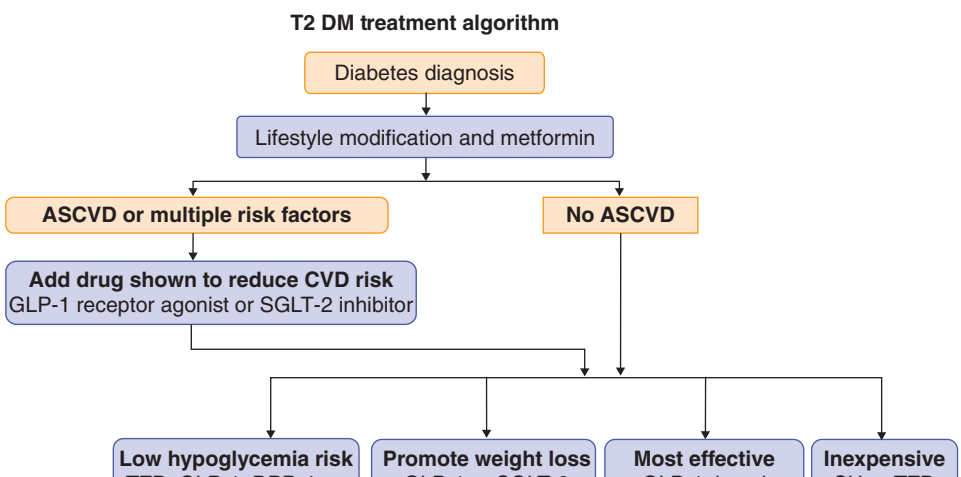

FIGURE 216-5. Algorithm for pharmacologic treatment of type 2 diabetes. ASCVD = Atherosclerotic cardiovascular disease; CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase 4; DPP-4-i = DPP-4 inhibitor; GLP-1 = glucagon-like peptide 1; HbA_{1c} = glycosylated hemoglobin; SGLT-2 = sodium-glucose cotransporter-2; SU = sulfonylurea; TZD = thiazolidinedione.

Incretin-Based Therapies/DPP-4 Inhibitors

Inhibitors of dipeptidyl peptidase 4 (DPP-4), a ubiquitous serine protease, work by preventing the breakdown of endogenous GLP-1, thus prolonging its effects. DPP-4 inhibitors, including sitagliptin, saxagliptin, and linagliptin, are given orally in a single daily dose. Similar to GLP-1 agonists, they rarely cause hypoglycemia, but they are generally weight neutral and cause fewer gastrointestinal side effects. In a large randomized trial of patients with preexisting CVD, sitagliptin had no effect on future cardiovascular events. A network meta-analysis has shown that the use of GLP-1 agonists (above) or SGLT2 inhibitors (below) were associated with lower all-cause mortality in patients with type 2 diabetes that DDP-4 inhibitors or placebo or no treatment.[17] Concern about potential risk of pancreatitis and medullary thyroid cancer has also been raised but unconfirmed; however, severe joint pain and skin reactions (bullous pemphigoid) can occur in a small percentage of patients.

Other Pharmacologic Agents

SGLT2 Inhibitors

Canagliflozin, dapagliflozin, and empagliflozin are inhibitors of the sodium glucose cotransporter 2 (SGLT2) in the proximal renal tubule. This inhibition prevents the reabsorption of filtered glucose and results in glycosuria, which is accompanied by mild osmotic diuresis and modest weight loss. The most common adverse effect is an increase in mycotic genital infections; hyperkalemia, urinary tract infections, and reductions in blood pressure have also been reported. Other adverse effects include increased risk of diabetic ketoacidosis, and for canagliflozin, lower extremity amputation. In a large randomized trial of type 2 diabetes patients at high risk for cardiovascular events, empagliflozin reduced cardiovascular and all-cause death by 32% when added to standard care. Similar cardiovascular benefit has been reported with canagliflozin, but with a greater risk of amputation, primarily at the toe or metatarsal level, and both drugs appear to prevent decline in renal function. Among patients with evidence of CKD (albuminuria and/or eGFR 30-90 ml/min), canagliflozin can reduce the risk of adverse renal outcomes by 30%.

Other Drugs

Acarbose and miglitol are inhibitors of α-glucosidase enzymes in the intestinal lumen. They are given with meals to slow the absorption of carbohydrates. Gastrointestinal side effects (e.g. flatulence and bloating) are common and limit their use. Pramlintide, bromocriptine, and colesevelam are also approved for treatment of type 2 diabetes. However, they are used infrequently due to side effects and modest glucose-lowering properties.

Insulin Therapy

Insulin treatment can be considered for patients with type 2 diabetes at any point in the course of the disorder, although typically it is used after "failure" of oral or other noninsulin therapies. Insulin may also be preferred therapy in specific situations, such as during hospitalizations (especially in the perioperative period) or in pregnancy. In contrast to patients with type 1 diabetes, patients with type 2 diabetes may be adequately controlled with basal insulin alone or in combination with other antidiabetic medications. Basal insulin is frequently used in combination with oral medications (e.g., metformin, DPP-4 inhibitors) or GLP-1 agonists (e.g., exenatide, liraglutide). However, reflecting the heterogeneity of type 2 diabetes, some patients may require physiologic insulin replacement similar to that used in type 1 diabetes, and insulin pump therapy is a safe and valuable option in patients who otherwise require multiple daily injections. Daily insulin requirements tend to be higher for patients with type 2 compared with type 1 diabetes, reflecting the existence of insulin resistance. Use of concentrated insulin preparations (U-200 degludec, U-300 glargine, U-500 regular, U-200 lispro) may be helpful for insulin resistant patients who require insulin doses exceeding 100 units per day. Among patients with type 2 diabetes at high risk for cardiovascular events (CVEs), degludec is noninferior to glargine with respect to the incidence of major CVE and reduces the risk of symptomatic hypoglycemia. Information about available insulin preparations and insulin regimens is provided in the section on insulin therapy under type 1 diabetes (earlier) and in Table 216-5.

Treatment Algorithms

Use of multidrug regimens is common in type 2 diabetes, and algorithms have been developed to guide therapy; however, the current evidence base to support these recommendations is limited. There is general agreement that metformin should be initial therapy for most patients and that subsequent drugs (when needed) are added to but do not replace metformin. The choice of a specific drug combination is driven by a number of factors, including efficacy, cost, side effect profile (e.g., hypoglycemia, weight gain), and preference of the patient (Fig. 216-5). Preferential use of drugs shown to have cardiovascular benefits should be considered for patients with established atherosclerotic heart disease or multiple cardiovascular risk factors.

Metabolic Monitoring

Ongoing assessment of glycemic control is necessary to ensure optimal outcomes in patients with diabetes. Measurement of HbA_{1c}, which reflects mean glucose levels during the preceding 2- to 3-month period, should be performed routinely in all patients with diabetes, beginning at diagnosis and periodically thereafter. Quarterly tests should be done for patients whose therapy has been recently changed or who are not meeting glycemic goals. More stable patients can be tested twice a year. Self-monitoring of blood glucose levels is recommended for all patients using insulin and may be useful for any patient trying to achieve target glucose control. Monitoring for the development of vascular complications is addressed in the later section on chronic vascular complications.

Inpatient Management

Management of blood glucose levels during hospitalization is increasingly recognized as an important clinical issue, especially because 40 to 70% of hospitalized patients carry a concomitant diagnosis of diabetes. Frequently, diabetes is not the reason for admission, and attention to glucose management is secondary to other more critical medical problems. However, both hyperglycemia and hypoglycemia are associated with adverse outcomes in hospitalized patients, which has stimulated the development of algorithms and guidelines for inpatient glucose management, although the evidence base to support them is limited. Obviously, all patients with type 1 diabetes require continued insulin use during hospitalization.

Critically Ill Patients

After initial enthusiasm for intensive glucose control (maintenance of near-normoglycemia) for critically ill patients, more recent evidence suggests that it may be harmful, particularly when it is accompanied by hypoglycemia. Current guidelines recommend intravenous administration of insulin for critically ill patients in intensive care settings, with a goal of maintaining plasma glucose concentration between 140 and 180 mg/dL. Application of

standardized infusion protocols, which include frequent glucose monitoring, is recommended.

Non–Critically Ill Patients

The evidence base to support specific treatment guidelines for non–critically ill hospitalized patients is weak because this has not been systematically studied in randomized trials. However, there is agreement that subcutaneous administration of insulin is the preferred therapy to control glucose for most hospitalized (non–critically ill) patients with diabetes. Generally accepted targets are below 140 mg/dL for fasting glucose concentration and below 180 mg/dL for random or postprandial glucose concentration, if this can be achieved with minimal hypoglycemia risk. The patient's status needs to be reassessed frequently and insulin doses adjusted as needed to maintain target glucose levels. Use of basal insulin (see Table 216-5) is sufficient for many type 2 patients, but some may require the addition of prandial or corrective doses of short-acting insulin. However, prolonged dependence on insulin "sliding scales" to manage hyperglycemia should be avoided as this is rarely successful and carries the increased risk of hypoglycemia. For stable patients who are eating consistent meals and those nearing hospital discharge, resumption of their usual oral or noninsulin injectable medications can be considered. Most patients with type 1 diabetes can be managed with their usual insulin injection regimen during hospitalization, but extra attention should be paid to hypoglycemia risk due to missed or delayed meals. Insulin pump therapy can be continued during hospitalization if the patient is able to direct its use and hospital personnel are sufficiently familiar with this form of treatment.

Prevention of Type 2 Diabetes

The substantial burden, both human and societal, that accompanies type 2 diabetes and the difficulty in treating it effectively once it has developed make it an appropriate target for prevention. Further, the existence of a defined state of increased risk, pre-diabetes (i.e., impaired glucose tolerance and impaired fasting glucose), allows identification of patients who are most likely to benefit. Interventions that have been studied to date include lifestyle change (i.e., weight loss and exercise) and several antidiabetic medications.[18]

LIFESTYLE CHANGES

The largest and longest diabetes prevention study to date was the Diabetes Prevention Program, conducted in the United States beginning in the 1990s. Individuals at high risk for type 2 diabetes on the basis of the presence of overweight or obesity and pre-diabetic hyperglycemia (fasting glucose concentration of 95 to 125 mg/dL and 2-hour glucose concentration of 140 to 199 mg/dL) were randomly assigned to an intensive lifestyle program or a medication arm (metformin vs. placebo) and observed for a mean of 3 years. The lifestyle intervention stressed modest weight reduction (minimum 7% of body weight) with a reduced fat, hypocalorie diet and moderate-intensity physical activity for 150 minutes/week. Incident diabetes (determined by oral glucose tolerance test) was reduced by 58% compared with placebo, although the risk reduction was somewhat diminished (34%) with longer-term follow-up of the cohort. Successful weight loss was the major predictor of diabetes prevention, with every kilogram of weight loss reducing diabetes risk by 16%. Primary care–led weight management programs and locaserin use can reduce hyperglycemia and lead to remission of type 2 diabetes. Similar findings were reported from other studies, including the Finnish Diabetes Prevention Study. Even among individuals who did not lose weight, achieving the physical activity goal was associated with lower diabetes risk.

MEDICATION

Several classes of antidiabetic drugs have been studied for diabetes prevention, including metformin, which reduced the risk of diabetes by 31% in the Diabetes Prevention Program. In smaller studies, the α-glucosidase inhibitor acarbose showed modest reduction in diabetes risk (approximately 25%). The thiazolidinediones (e.g., troglitazone and rosiglitazone) have also shown diabetes prevention effects but are not widely used for this purpose because of concerns about their long-term safety. Liraglutide used at the dose approved for weight loss (3 mg/day) lowered incident diabetes by 21% in overweight patients with pre-diabetes. None of these drugs is approved by the U.S. Food and Drug Administration for diabetes prevention.

RECOMMENDATIONS

Lifestyle modification and metformin can both be recommended for individuals at high risk of diabetes. Candidates for prevention include those with defined glucose abnormalities (impaired glucose tolerance, impaired fasting glucose) and those with overweight or obesity plus an additional risk factor, such as family history of diabetes. The curriculum for the lifestyle intervention used in the Diabetes Prevention Program is available online (http://www.bsc.gwu.edu/dpp/lifestyle/dpp_part.html) and has been widely implemented in community settings, including the YMCA. Both lifestyle modification and metformin have shown positive effects on cardiovascular risk factors, but whether interventions to prevent diabetes will result in lower rates of microvascular or macrovascular complications remains to be determined.

TABLE 216-8 CRITERIA FOR DIABETES SCREENING IN ASYMPTOMATIC ADULTS

1. Overweight or obese (BMI >25 kg/m^2) with one or more of the following:
   - First-degree relative with type 2 diabetes
   - High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of CVD
   - Hypertension
   - HDL cholesterol level <35 mg/dL or triglyceride level >250 mg/dL
   - Women with polycystic ovary syndrome
   - Physical inactivity
   - Other clinical conditions associated with insulin resistance

   Screening should begin at age 45 and be repeated at least every 3 years.
2. Patients with pre-diabetes (HbA_{1c} ≥5.7%, IGT, or IFG) should be tested annually.
3. Women with history of gestational diabetes should be tested at least every 3 years.

BMI = body mass index; HDL = high-density lipoprotein; IFG = impaired fasting glucose; IGT = impaired glucose tolerance.
Modified from American Diabetes Association. Standards of medical care in diabetes—2018. *Diabetes Care*. 2018;41(Suppl 1):S55-S64.

Screening for Type 2 Diabetes

Individuals with risk factors for type 2 diabetes should be considered for screening for diabetes and impaired glucose regulation, even though screening has not been shown to reduce subsequent mortality.[19,20] This is especially important given that hyperglycemia can be present for years without specific symptoms and up to 30% of people with diabetes in the United States are undiagnosed. Screening will also allow identification of people with pre-diabetes, who may benefit from prevention interventions (Table 216-8).

Diabetes screening may be conducted with HbA_{1c} level, fasting glucose concentration, or oral glucose tolerance test, with the choice of test depending on the clinical setting and the preference of the patient. Screening should also be considered for asymptomatic children with BMI above the 85th percentile for age and sex plus any two of the following risk factors: family history of type 2 diabetes, high-risk race/ethnicity, or evidence of insulin resistance or features associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational-age birth weight). Pregnant women with risk factors for diabetes should be screened for undiagnosed diabetes at the first prenatal visit. Otherwise, a 75-g oral glucose tolerance test should be performed at 24 to 28 weeks of gestation to detect gestational diabetes.

Prognosis

Type 2 diabetes is a chronic and, in most cases, progressive condition with potentially serious health consequences. However, it is also uniquely sensitive to modification of nutritional and lifestyle factors, which has been shown to be effective for both prevention and treatment of diabetes. Further, several classes of effective antihyperglycemic medications are available. There is substantial evidence that early intervention with a multifactorial approach to achieve and to maintain metabolic control, plus aggressive control of CVD risk factors, will substantially reduce the burden of diabetes complications and improve quality of life.

ACUTE METABOLIC COMPLICATIONS OF DIABETES

Hypoglycemia

Iatrogenic hypoglycemia in people with diabetes is the most frequent cause of low blood glucose concentration. Hypoglycemia (Chapter 217) affects the daily lives of persons with diabetes and can have a dramatic effect on quality of life. It can induce great fear, preclude comfortable engagement in routine activities (e.g., driving, uninterrupted sleep), and lead both patient and clinician to set higher glycemic targets and hence worse metabolic control. Thus hypoglycemia continues to be a major limiting factor in the treatment of diabetes, particularly with the use of insulin.[21]

Whereas insulin-stimulatory drugs (e.g., sulfonylureas) and parenteral insulin are the primary causes of drug-induced iatrogenic hypoglycemia, underlying

defects in some parts of the counter-regulatory cascade contribute to the greater frequency and potential morbidity and mortality of hypoglycemia among patients with diabetes. The normal counter-regulatory response to hypoglycemia and the typical adrenergic and neuroglycopenic hypoglycemia symptoms are described in Chapter 217.

The threshold plasma glucose value that results in hypoglycemic symptoms is not constant; it is lower after recent antecedent hypoglycemia and higher in patients with poor glycemic control. However, there is general consensus that a self-monitored glucose level of 70 mg/dL or lower is a value that should alert the patient or caregiver, regardless of the presence of symptoms. A more detailed classification system to describe hypoglycemia has been established and widely adopted in research settings (Table 216-9).

However, these distinctions are not commonly used in clinical practice, and the severity of symptoms is often confused with severity of the actual prevailing physiologic state. Thus a patient may feel intense symptoms at a glucose level of 50 to 60 mg/dL, for which there is no evidence of cognitive impairment or imminent danger, whereas potentially dangerous plasma glucose levels in the range of 20 to 40 mg/dL might go unappreciated owing to lack of classical symptoms. This also has implications for the epidemiology of hypoglycemia; most studies have reliably ascertained only the rates of severe hypoglycemia because other episodes are less likely to be documented. In type 1 diabetes, the DCCT reported 62 severe hypoglycemic episodes per 100 patient-years, although the actual risk may be higher in clinical settings. An episode of severe hypoglycemia can be the immediate cause of death in patients with type 1 diabetes, with recently reported mortality rates ranging from 4 to 10%. There remains uncertainty about the temporal relationship between hypoglycemia and death, and although prolonged episodes of very low circulating glucose (<15 mg/dL) can cause brain death, episodes of fatal hypoglycemia may be due to other mechanisms, such as ventricular arrhythmias. Episodes of severe hypoglycemia are much less common in patients with type 2 diabetes (see later).

In patients with treated diabetes, the initiation of the hypoglycemic event is due to mismatching of prevailing insulin levels to the underlying physiologic state of the individual. Thus even absent overt insulin overdosage, factors such as missed meals, exercise, recent weight loss, alcohol, or insulin-sensitizing drugs create this mismatch and may set the plasma glucose concentration on a downward trajectory. In addition, the counter-regulatory systems that normally would counteract the decline of glucose to dangerous levels may be impaired. In patients with type 1 diabetes, glucagon release during hypoglycemia may become impaired shortly after the onset of diabetes, although glucagon is still secreted in response to other secretagogues, suggesting the presence of a functional defect. Epinephrine release during hypoglycemia also becomes progressively defective in type 1 diabetes; it is not triggered until the plasma glucose level is lower, and the maximal concentration of epinephrine released is significantly reduced. This decrease in epinephrine response during hypoglycemia is accompanied by an attenuated autonomic neural response, which results in the clinical syndrome of *impaired awareness of hypoglycemia*. Without autonomic symptoms, mild hypoglycemia may proceed unnoticed to more advanced and dangerous phases. Patients who have both impaired awareness of hypoglycemia and defective counter-regulation are at the greatest risk for development of severe hypoglycemia.

Hypoglycemia-associated autonomic failure in type 1 diabetes apparently results from antecedent episodes of mild hypoglycemia that further degrade the counter-regulatory response. In experiments in people without diabetes, recurrent or recent episodes of hypoglycemia are associated with reduced autonomic (epinephrine and norepinephrine), symptomatic, and cognitive functional responses to subsequent episodes of hypoglycemia, impairing the endogenous defense mechanisms and the clinical signs required for hypoglycemia detection. Because patients with type 1 diabetes already have a reduced counter-regulatory response, hypoglycemia-associated autonomic failure may play a role in the vicious circle of hypoglycemia begetting hypoglycemia. Meticulous avoidance of hypoglycemia is the only current approach proven to improve the epinephrine response and to reverse impaired awareness of hypoglycemia.

Compared with type 1 diabetes, type 2 diabetes is associated with a much lower risk of hypoglycemia. However, hypoglycemia remains a major clinical problem in this population. Episodes of severe hypoglycemia become progressively more common in patients with longer duration of type 2 diabetes, due in part to progressive β-cell failure and increased dependence on pharmacologic treatments. Use of sulfonylureas accounts for a substantial proportion of cases of drug-induced hypoglycemia, and severe episodes characterized by coma have been reported with all the agents in common use. Other antidiabetic agents, such as metformin, thiazolidinediones, and incretin-based drugs, have been associated with measureable albeit lower risks of hypoglycemia; however, symptomatic hypoglycemia is rare unless these drugs are used in combination with insulin. The elderly are at particularly high risk for iatrogenic hypoglycemia because the intensity of adrenergic symptoms may be reduced and hypoglycemia-induced cognitive impairment greater.

TABLE 216-9 CLASSIFICATION OF IATROGENIC HYPOGLYCEMIA IN TREATED DIABETIC PATIENTS

	CLINICAL FEATURES
Severe hypoglycemia	Episode with neurocognitive impairment that requires another person to administer treatment
Documented symptomatic hypoglycemia	Measured glucose concentration ≤70 mg/dL that coincides with sympathoadrenal or neurologic symptoms. Episode is self-managed.
Asymptomatic hypoglycemia	Measured glucose concentration ≤70 mg/dL, but without concomitant symptoms. Absence of symptoms may be due to hypoglycemia unawareness or hypoglycemia-associated autonomic failure.
Pseudo-hypoglycemia	Typical hypoglycemia symptoms, but with measured glucose concentration >70 mg/dL. Symptoms may be caused by resetting of counter-regulatory system in the setting of chronic poor glucose control.

CLINICAL APPROACH TO HYPOGLYCEMIA PREVENTION AND TREATMENT

Rx

Patients with diabetes need to be well informed about the symptoms of hypoglycemia and the factors that predispose to its occurrence: meal timing and content, exercise, and the expected time course of the drugs in use (especially insulin). Patients should also be made aware that the accuracy of some home glucose meters and continuous glucose monitors may be reduced in the hypoglycemia range and that the typical sympathoadrenal symptoms may wane during years of diabetes. A history of recurrent hypoglycemia should be carefully evaluated and attempts made to determine whether the patient had experienced events that went unrecognized. For example, reports of unexplained night sweats or a clouded mental state on arising in the morning may be due to nocturnal hypoglycemia and should be investigated.

Table 216-10 lists several risk factors for severe hypoglycemia. Patients with these characteristics require greater vigilance, both in selection of treatment regimen and in the recognition and treatment of acute episodes.

Most mild or moderate episodes of hypoglycemia can be self-treated by ingestion of fast-acting carbohydrates such as glucose tablets, glucose gels, or food (juices, soft drinks, or a meal). The suggested amount of carbohydrate to be ingested is about 15 g, which will increase the plasma glucose concentration by about 15 mg/dL. Importantly, foods that are rich in fat delay glucose absorption and are thus less effective. If plasma glucose levels are still below 70 mg/dL and if symptoms have not abated after 15 minutes, the patient should take an additional 15 g of carbohydrate. Because the glycemic response to oral glucose is relatively transient, ingestion of a snack or a meal shortly after correction of hypoglycemia is recommended.

Parenteral treatment of hypoglycemia is recommended if the patient is unwilling or unable to ingest carbohydrates (e.g., due to impaired mental status) or if a patient has sulfonylurea-induced hypoglycemia (which may be prolonged). Intravenous administration of glucose (25 g) is the preferred treatment of hypoglycemia. Parenteral glucagon (1 mg subcutaneously) is an alternative, especially in patients with type 1 diabetes who may have to be treated by

TABLE 216-10 RISK FACTORS FOR SEVERE HYPOGLYCEMIA IN PATIENTS WITH DIABETES

Youth (children)
Elderly taking sulfonylurea drugs or insulin
Altered consciousness
Ethanol use
Strenuous exercise in the previous 24 hours
Recent antecedent hypoglycemia
Use of pentamidine, quinine, or nonselective β-blocker drugs
Concomitant illnesses, such as sepsis, or hepatic, renal, or cardiac failure
Type 1 diabetes with history of recurrent severe hypoglycemia
Recent rapid improvement in HbA_{1c} into the normal range

family members for severe hypoglycemia. Because glucagon stimulates secretion of insulin in addition to promoting glucose production, it is less effective in patients with type 2 diabetes.

Nocturnal hypoglycemia may be a particular problem for patients with type 1 diabetes. It may be asymptomatic and unsuspected because plasma glucose concentration is rarely measured during the night. Risk factors for nocturnal hypoglycemia include increased physical activity in the last 24 hours, certain insulin regimens (e.g., use of NPH or regular insulin), meal content (e.g., the amount of fat), and alcohol consumption. In addition, sleep is associated with a decrease in the autonomic response to hypoglycemia. Currently, the only practical approaches to detection of nocturnal hypoglycemia are regular nocturnal (3 AM) self-monitoring or the use of continuous glucose monitors with alarm features. Some patients with nocturnal hypoglycemia present with sleep disturbances, morning headache, chronic fatigue, or depression. Children in particular may present with seizures or enuresis. Strategies to prevent nocturnal hypoglycemia include eating "long-acting" bedtime snacks (slowly absorbed carbohydrate, such as uncooked cornstarch) and regular monitoring of blood glucose concentration at bedtime so that corrective action (carbohydrate ingestion) can be taken.

Hyperglycemic States

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS) are the most serious acute hyperglycemic complications of diabetes. DKA is typically associated with severe insulin-deficient states (i.e., type 1 diabetes). It may also occur rarely in type 2 diabetes under conditions of extreme stress, such as major infection or trauma or as a presentation of a variant of type 2 diabetes (ketosis-prone or Flatbush diabetes). On the other hand, HHS typically occurs in patients with type 2 diabetes. However, the distinction between the two clinical scenarios is sometimes blurred (e.g., patients with HHS may present with ketosis and acidosis), and these states may be considered as parts of the spectrum of severe metabolic decompensation. Despite aggressive treatment, mortality rates remain high for both conditions, approaching 5% for DKA and 15% for HHS. Mortality is associated not only with the extremes of age (i.e., the very young and the elderly) and comorbidities but also, importantly, with the severity of the precipitating illness or event. Thus in addition to correction of fluid and electrolyte imbalance and administration of insulin, treatment also includes prompt recognition of and therapy for any precipitating illness or event. A list of precipitating conditions commonly associated with DKA and HHS is shown in Table 216-11.

PATHOBIOLOGY

The pathogenesis of DKA and HHS mirrors the underlying respective forms of diabetes. The three fundamental biochemical features of DKA—hyperglycemia, ketosis, and acidosis—result from the combined effects of deficient circulating insulin and counter-regulatory hormone excess. This hormonal milieu promotes the delivery of substrates from muscle (amino acids, lactate, pyruvate) and adipose tissue (free fatty acids, glycerol) to the liver, where they are converted to glucose or to ketone bodies (β-hydroxybutyrate, acetoacetate, acetone). Glucose and ketones are thus released into the circulation at greater rates than their utilization, resulting in severe hyperglycemia (>250 mg/dL), ketoacidosis (arterial pH <7.30), and an osmotic diuresis that promotes dehydration and electrolyte loss. In HHS, despite comparable elevations of glucagon, the presence of some endogenous insulin modulates the ketosis even though the plasma glucose concentration in HHS typically exceeds 600 mg/dL, whereas in DKA it is usually more than 250 mg/dL.

In both states, fluid depletion plays a major role in causing dramatic elevations in circulating glucose. Indeed, the hyperosmolality accompanying DKA and HHS is best linked to the patient's level of neural and cognitive function, and treatment of both conditions depends on restoration of fluid balance. Finally, other factors have been invoked, including other hormones (such as epinephrine, growth hormone, and cortisol), proinflammatory cytokines (such as tumor necrosis factor–α, interleukin-1β, interleukin-6, and interleukin-8), and lipid peroxidation markers as well as plasminogen activator inhibitor–1 and C-reactive protein. Whether all these factors are simply "stress markers" reflecting the disordered metabolic state or true pathogenetic factors remains uncertain.

TABLE 216-11 PRECIPITANTS OF DIABETIC KETOACIDOSIS AND HYPEROSMOLAR HYPERGLYCEMIC STATE

MOST COMMON
Inadequate insulin treatment or noncompliance
New-onset diabetes
Infections
Myocardial infarction
OTHER PRECIPITATING FACTORS
Cerebrovascular accident
Acute pulmonary embolism
Acute pancreatitis
Intestinal or mesenteric thrombosis
Alcohol intoxication
Endocrinopathies: Cushing syndrome, thyrotoxicosis, acromegaly
Severe burns, hyperthermia, hypothermia
Drugs: clozapine, olanzapine, cocaine, lithium, sympathomimetics, corticosteroids, thiazide diuretics, SGLT-2 inhibitors

SGLT-2 = sodium-glucose cotransporter-2.

Diabetic Ketoacidosis

CLINICAL MANIFESTATIONS

DKA (Chapter 110) may signal the onset of type 1 diabetes, but changes in medical practice in the developed world during the past several decades have enhanced earlier diagnosis of type 1 diabetes, and now the majority of childhood cases are detected and treated before ketoacidosis occurs. Thus DKA is more frequently seen in those with established diabetes, usually in the setting of coexisting illness or poor adherence. For example, a patient may be unable to maintain adequate hydration during an illness, such as a viral gastroenteritis, and may mistakenly omit insulin because of inability to eat. A key component of a diabetes treatment program is education in "sick-day" rules focused on home-based prevention of DKA (e.g., frequent blood glucose monitoring, serum or urine ketone testing, fluid intake, determination of insulin dosing or delivery problems). Behavioral factors may also be involved; some younger patients may omit insulin deliberately to promote weight loss or to call attention to a dysfunctional home situation. This should be suspected in cases of recurrent episodes of DKA.

The clinical history of DKA typically involves deterioration during several hours to days, with progressive polyuria, polydipsia, and other symptoms of hyperglycemia. Other common clinical features are weakness, lethargy, nausea, and anorexia. Nonlocalizing upper abdominal pain in the setting of DKA can mimic an acute abdomen. Reduced motility of the gastrointestinal tract or, in severe cases, paralytic ileus may further contribute to diagnostic confusion. Nausea and vomiting are symptoms that indicate the need for in-hospital treatment because they preclude oral fluid intake. Physical findings in DKA are mainly secondary to dehydration, hyperosmolality, and acidosis; these include dry skin and mucous membranes, reduced jugular venous pressure, tachycardia, orthostatic hypotension, depressed mental function, and deep, rapid respirations (Kussmaul breathing).

DIAGNOSIS

In DKA, glucose levels may vary from modestly elevated to more than 1000 mg/dL, serum bicarbonate concentration drops below 18 mEq/L, and there is an excess anion gap that is generally proportional to the decrease in serum bicarbonate (Table 216-12). Hyperchloremia may be superimposed if the patient maintains an adequate GFR and is able to exchange keto acids for chloride in the kidney. The degree of depression of arterial pH depends largely on respiratory compensation. In mild cases, the pH may range from 7.20 to 7.30; in severe cases, it can fall below 7.00. On occasion, a degree of superimposed metabolic alkalosis (e.g., caused by vomiting or diuretic use) may obscure the true severity of the ketoacidosis. An anion gap out of proportion to the fall of bicarbonate should suggest this possibility. Other laboratory abnormalities commonly seen in DKA include a reduced measured serum sodium concentration (due to hyperosmolarity and the resulting osmotic shift of intracellular water into the intravascular space), prerenal azotemia, and elevated serum amylase. The last is usually of nonpancreatic origin and can lead to an erroneous diagnosis of pancreatitis. Normal, elevated, or reduced concentrations of potassium, phosphate, and magnesium may exist when DKA is diagnosed; however, large deficits of these electrolytes invariably accompany the osmotic diuresis and become readily apparent during the course of treatment. The serum triglyceride concentration is frequently elevated, a reflection of deranged lipid metabolism in the setting of insulin deficiency. The white blood cell count is typically elevated; the hemoglobin and hematocrit may be elevated, reflecting intravascular volume contraction (hemoconcentration).

Special care should be taken in interpreting serum or urine ketone results. Because quantitative measurements of β-hydroxybutyrate and acetoacetate

TABLE 216-12 DIAGNOSTIC CRITERIA FOR DIABETIC KETOACIDOSIS (DKA) AND HYPEROSMOLAR HYPERGLYCEMIC STATE (HHS)

CRITERION	MILD DKA	MODERATE DKA	SEVERE DKA	HHS
Plasma glucose concentration (mg/dL)	≥250	≥250	≥250	≥600
Effective serum osmolality (mOsm/kg)	Variable	Variable	Variable	≥320
Urine or serum ketones (nitroprusside reaction)	Positive	Positive	Positive	Negative to small
Arterial pH	7.25-7.30	7.00-7.24	<7.00	>7.30
Serum bicarbonate (mEq/L)	15-18	10-15	<10	>15
Anion gap (mEq/L)	>10	>12	>12	Variable, usually <12
Typical mental status	Alert	Drowsy	Stupor or coma	Stupor or coma

are not readily available, rapid diagnosis usually requires qualitative assessment of serum ketones by the use of serum dilutions and reagent strips (e.g., Ketostix) or tablets (e.g., Acetest), which depend on a nitroprusside reaction with acetoacetate. However, acetone reacts weakly with nitroprusside, and β-hydroxybutyrate does not react at all; thus the results of qualitative testing for ketones can be misleadingly low. Furthermore, because of the presence of intracellular acidosis, β-hydroxybutyrate levels are often much higher than acetoacetate levels, which may further conceal the true degree of ketoacidosis. Conversely, after insulin therapy is begun, the nitroprusside reaction may give the "false" impression of sustained ketoacidosis for hours or even days. This occurs because nonacidic acetone is slowly cleared from the circulation and also because, as acidosis improves, β-hydroxybutyrate is converted to acetoacetate, giving the false impression that ketosis is worsening.

TREATMENT

Rx

An overview of the treatment of DKA and HHS is shown in Figure 216-6.

In the early hours of treatment, the primary considerations are to restore intravascular volume, to correct tissue hypoperfusion, and to restore insulin sensitivity. With DKA, large total body deficits of water (5 to 10 L), sodium (5 to 10 mEq/kg), and other electrolytes may exist (Chapter 110). These losses are even more profound in HHS, which typically develops during a longer time. Although water loss usually exceeds the loss of sodium, it is almost always preferable to begin fluid replacement with isotonic normal saline (0.9% NaCl solution) for efficient intravascular volume restoration. Fluid replacement regimens vary, but it is common to administer 1 L of normal saline within the first hour, followed by a continuous infusion with either 0.45% NaCl or 0.9% NaCl, depending on the corrected serum sodium concentration, the patient's hemodynamic status, and the clinical assessment of tissue perfusion. Likewise, the rate of infusion (commonly 250 to 500 mL/hour) should be adjusted according to both biochemical responses and the age and clinical status of the patient (e.g., oliguria or underlying CVD). In children, isotonic solutions are generally preferred because they are less likely than hypotonic solutions to accelerate water shifts into the intracellular space and contribute to cerebral edema. As the blood glucose concentration falls below 250 mg/dL, dextrose should be added to intravenous fluids to avoid later insulin-induced hypoglycemia because continued insulin delivery may be required to correct the persistent acidemia.

Although insulin resistance is present in both DKA and HHS, supraphysiologic doses of insulin are unnecessary and are more likely to provoke hypokalemia, hypophosphatemia, and delayed hypoglycemia. A typical insulin replacement regimen uses an intravenous 0.1 U/kg bolus of rapid-acting (e.g., regular) insulin, followed by 0.1 U/kg/hour thereafter. Intravenous administration is the most predictable way to deliver insulin to target tissues, particularly in severely hypovolemic patients with reduced peripheral blood flow. If intravenous administration is not possible, intramuscular or subcutaneous routes of administration can be used. It is ideal if blood glucose levels fall at a steady and predictable rate (50 to 75 mg/dL/hour), so it is important to monitor blood glucose levels hourly during insulin therapy to ensure an appropriate rate of decline. Blood glucose levels should not fall too rapidly, especially in young children, in whom accelerated correction of plasma glucose concentrations has been associated with cerebral edema.

After a stable blood glucose level of 150 to 250 mg/dL is achieved, with resolution of the anion gap acidosis, subcutaneous administration of insulin can be started and the intravenous insulin infusion discontinued. With DKA, it is important to overlap the intravenous and subcutaneous routes by at least 1 to 2 hours to avoid the rebound ketoacidosis if insulin levels drop precipitously. After stabilization, and with resumption of oral food intake, long-term medical management should be initiated (or resumed), with both long-acting and short-acting insulins, to approximate the desired outpatient regimen. A temporary "regular insulin sliding scale" should be avoided because such therapy is reactive to hyperglycemia and the swings in glycemia will not allow safe discharge of the patient. The eventual dosage and frequency of insulin depend on multiple factors, including body weight, comorbidity, insulin sensitivity, and effectiveness of prior therapeutic regimens.

Potassium replacement is usually required in DKA. Overt hypokalemia can result in muscle weakness, cramps, and nausea; both hyperkalemia and hypokalemia are associated with cardiac arrhythmias. Even absent severe hypokalemia, patients have a significant total body potassium deficit (about 3 to 7 mEq/kg), and measured serum potassium levels may be normal or high as acidosis and renal failure can mask the potassium deficiency. As insulin is infused, potassium will move into the intracellular space, further lowering serum potassium to levels that may trigger life-threatening arrhythmias. In addition, fluid replacement causes extracellular dilution of potassium, leading to improved renal perfusion and increased urinary potassium excretion. Thus potassium replacement should be initiated as soon as it is established that the patient is not in renal failure. A low potassium level (<3.5 mEq/L) requires prompt treatment with up to 40 mEq/hour, whereas "normal" serum levels (3.5 to 5.0 mEq/L) call for less aggressive repletion of potassium (20 to 30 mEq/hour), assuming adequate urine output. In patients who may have lost potassium for additional reasons, such as diuretic use or gastrointestinal loss, there will be need for greater potassium supplementation.

In the majority of patients with mild to moderate DKA, keto acids clear spontaneously with standard therapeutic measures, and correction of the pH with alkali (as bicarbonate) is unnecessary. Suppression of lipolysis by insulin reduces free fatty acid flux to the liver and blocks ketogenesis, and circulating keto acids are then cleared or oxidized, with subsequent regeneration of bicarbonate and restoration of arterial pH. However, in cases of severe acidosis (pH <6.9 to 7.0), bicarbonate administration may be indicated if the clinical picture dictates (e.g., hypotension that is unresponsive to fluids, cardiac dysfunction, respiratory exhaustion).[22] Bicarbonate therapy should be used with caution and only at the minimal doses required to stabilize the patient because it can further provoke hypokalemia. In addition, by causing a sudden left shift of the dissociation curve for oxyhemoglobin, bicarbonate may impair oxygen delivery to the tissues. Therefore if alkali therapy is given, small amounts should be administered slowly: 50 mEq of $NaHCO_3$ during 1 hour for arterial pH 6.9 to 7.0, and 100 mEq during 2 hours for pH below 6.9. After bicarbonate administration, arterial pH (and serum potassium levels) should be rechecked every 2 hours, and alkaline therapy should be discontinued when the pH rises above 7.0.

In the setting of DKA, phosphate losses average 3 to 7 mmol/kg; magnesium losses reach 1 to 2 mEq/kg. Phosphate is shifted extracellularly during hyperosmolar states, so initial serum levels may be falsely elevated and may drop rapidly during therapy. Complications of hypophosphatemia generally occur at serum levels below 1.0 mg/dL and include respiratory and skeletal muscle weakness, impaired cardiac systolic performance, and hemolytic anemia. Phosphate repletion should be used in patients with serum phosphate levels below 1.0 mg/dL and in patients with evidence of cardiac or respiratory compromise, hypoxia, or hemolytic anemia. An effective means of replacing phosphate is to replace one third to one half of the potassium losses (discussed previously) as potassium phosphate. In severe hypophosphatemia, cautious intravenous administration of additional small amounts of potassium phosphate may be necessary. Because of calcium binding, hypocalcemic tetany may complicate phosphate therapy unless magnesium supplements are also provided; for this reason, serum calcium, phosphate, and magnesium levels should be monitored during any phosphate infusion.

Hyperosmolar Hyperglycemic Syndrome

CLINICAL MANIFESTATIONS

The metabolic state formerly known as the hyperglycemic hyperosmolar nonketotic state or coma has been renamed the *hyperosmolar hyperglycemic syndrome* (HHS) to highlight two important points: (1) ketosis (and acidosis) may in fact be present to varying degrees in HHS, and (2) alterations in sensorium most commonly occur in the absence of coma. In fact, only 10% of HHS patients present with frank coma, and an equal percentage show no signs whatsoever of mental status change. Major risk factors for HHS include older

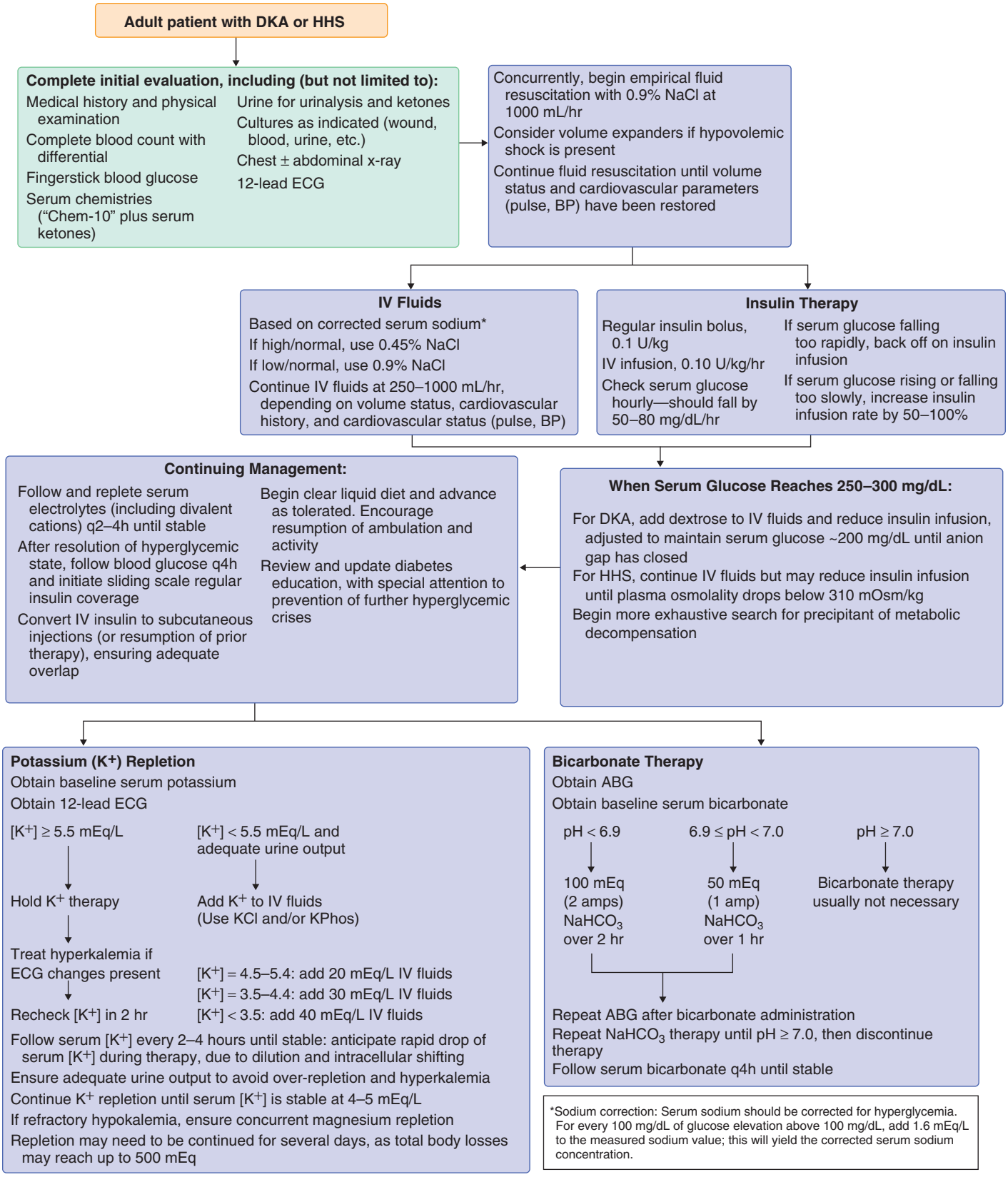

FIGURE 216-6. **Management of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic syndrome (HHS).** ABG = arterial blood gas; BP = blood pressure; ECG = electrocardiogram; IV = intravenous.

age (most cases occur in patients aged 65 years and older) and impaired cognition (i.e., impaired ability to recognize thirst or to obtain access to water).

As shown in Table 216-12, the hallmarks of the HHS are severe hyperosmolarity (>320 mOsm/L) and hyperglycemia (>600 mg/dL). Severe hyperglycemia occurs because patients cannot consume enough liquid to keep pace with a vigorous osmotic diuresis. The resulting impairment in renal function eventually further reduces glucose excretion through the kidney, leading to remarkable blood glucose elevations, sometimes exceeding 1000 mg/dL. In contrast to DKA, even though glucose concentrations are generally higher, severe acidosis and ketosis are usually absent in the HHS. This is probably explained by the presence of some residual insulin secretory capacity that is sufficient to suppress lipolysis and to avoid significant keto acid production. Some type 2 patients with depressed endogenous insulin secretion may be unable to suppress ketone production fully in the face of elevated counterregulatory hormones produced by physical illness. However, because HHS patients have higher portal vein insulin concentrations than do patients with

DKA, keto acid production by the liver is quantitatively less, yielding only mild acidosis. In the HHS, in the absence of concurrent acid-base disturbances, arterial pH rarely drops below 7.30, and serum bicarbonate levels typically do not fall below 18 mEq/L.

In the HHS, clinical severity and levels of consciousness generally correlate with the severity and duration of hyperosmolarity. Clinical signs indicate profound dehydration; gastrointestinal symptoms are seen less frequently than in DKA. A variety of often reversible neurologic abnormalities may exist, including grand mal or focal seizures, extensor plantar reflexes, aphasia, hemisensory or motor deficits, and worsening of a preexisting organic mental syndrome. The laboratory picture is dominated by the effects of uncontrolled diabetes and dehydration; renal function is impaired, hemoglobin and hematocrit are elevated, and liver function test results may be abnormal because of baseline hepatic steatosis. Although severe hyperglycemia would be expected to lower measured serum sodium concentration, it is not uncommon to see normal or even elevated sodium levels because of the severity of dehydration. The serum osmolarity can be measured directly or estimated.

TREATMENT

The approach to treatment of HHS is similar to that of DKA and requires aggressive management of fluids and electrolytes (see Fig. 216-6).[23] Importantly, patients with HHS tend to have more dramatic volume contraction, and by definition, acidosis is not present or is minimal in degree. It is important to volume resuscitate the patient adequately before insulin is administered because intracellular fluid shifts that occur as glucose levels are reduced may worsen systemic tissue perfusion. In fact, glucose levels usually drop substantially with hydration alone, in part because of improved renal perfusion, thus promoting glycosuria. Coadministration of dextrose along with insulin, as is recommended in patients with DKA to allow ketones to clear and the acidosis to resolve, is rarely required. Further, because recurrent acidosis is less of a concern, patients may be transitioned directly from insulin infusion to subcutaneous injections. Because altered mental status (and, in some cases, coma) is a frequent feature of HHS, attention should be paid to respiratory status and appropriate airway protection. A diligent search for underlying precipitating illness should be made, keeping in mind that the typical HHS patient is elderly and may well have overt or subclinical CVD. The presence of impaired cardiac function, also more common among the elderly, needs to be considered in the management of intravenous fluid resuscitation.

After resolution of the HHS episode, some patients may ultimately be able to be managed with oral agents alone. However, the development of HHS signifies a significant degree of insulin deficiency. As a consequence, it is always best to prescribe insulin injections before the patient is discharged and to reserve judgment about the appropriateness of using non-insulin therapies until the patient's progress can be monitored and reassessed in the outpatient setting.

CHRONIC VASCULAR COMPLICATIONS

Epidemiology

The major clinical burden associated with long-standing diabetes is the development of vascular disease, which includes characteristic microvascular complications (retinopathy, nephropathy, neuropathy) and accelerated medium- and large-vessel atherosclerosis. Diabetes is the leading cause of kidney failure, nontraumatic lower limb amputations, and new cases of blindness among adults in the United States. Diabetes is also a major cause of coronary heart disease, heart failure, and stroke and is the seventh leading cause of death in the United States. The microvascular complications are directly linked to hyperglycemia, with both the duration of diabetes and the degree of glucose elevation constituting the major risk factors. Other factors, including genetic susceptibility, smoking, and concomitant conditions like hypertension, also contribute to the risk of complications (Fig. 216-7). Diabetic microvascular complications occur in both type 1 and type 2 diabetes; given that most patients with type 1 diabetes develop it when younger, they may face greater lifetime risk of complications.

The central role for hyperglycemia in the development of diabetic complications was long suspected and ultimately confirmed by the landmark DCCT, which was reported in 1993. In this study, 1441 adolescents and younger adults with type 1 diabetes were randomly assigned to conventional treatment designed to avoid symptomatic hypoglycemia or hyperglycemia (standard therapy at the time) or to an experimental treatment group designed to achieve near-normoglycemia. The experimental group received intensive management with multiple daily insulin injections or use of a continuous subcutaneous insulin pump; frequent self-monitored blood glucose determinations; and adoption of detailed algorithms to guide the patient in determining insulin dosing in response to meals, glucose, and exercise. During the course of the study, mean HbA_{1c} levels were 7.2% in the intensive group compared with 9% for the conventional treatment group. The unequivocal DCCT results showed substantially lower rates of retinopathy, nephropathy, and neuropathy in the intensively treated group and led to major changes in the approach to diabetes treatment in the United States and worldwide. Results of the UKPDS, conducted in a cohort of recently diagnosed patients with type 2 diabetes, later confirmed the benefits of more intensive glucose control in the prevention of microvascular complications. These and other studies have provided convincing evidence that hyperglycemia is the driving force behind diabetic microvascular disease. Indeed, the long-term follow-up studies of the DCCT cohort showed that the benefits seen in the intensively treated group persisted for at least a decade after the study ended, even after HbA_{1c} levels between the two treatment groups converged, suggesting that the mechanisms underlying microvascular complications are conditioned by the prevailing metabolic milieu.

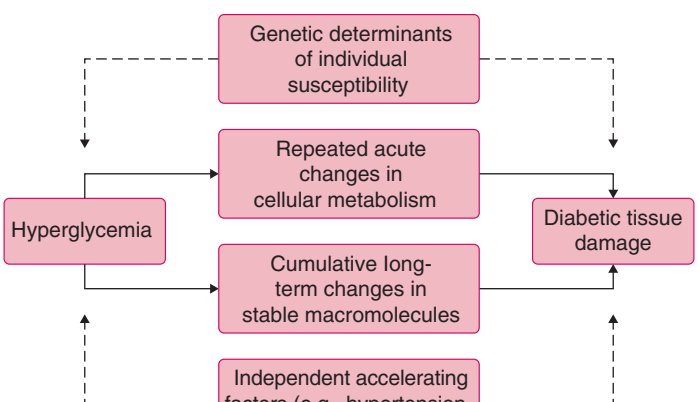

FIGURE 216-7. Factors related to the pathogenesis of diabetes complications. (From Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes.* 2005;54:1615-1625.)

Pathobiology

The cellular and molecular mechanisms that mediate hyperglycemic tissue damage are complex and still being elucidated. We now know that multiple interrelated pathways are involved, including four that have received the most attention as key mediators of vasculopathy (Fig. 216-8).

ADVANCED GLYCATION END PRODUCTS

Advanced glycation end products (AGEs) are a heterogeneous group of compounds that form by the nonenzymatic interaction of glucose with amino groups on proteins. This process occurs continuously in vivo but is markedly accelerated in the presence of hyperglycemia. Indeed, the HbA_{1c} test to monitor the chronic level of glycemia was the result of observations of the glycosylation of subfractions of adult hemoglobin. Levels of AGEs in serum and tissues (e.g., skin collagen) correlate with diabetic vascular complications and mean glucose levels over time. AGEs can alter the properties and function of long-lived proteins, such as collagen and elastin, leading to vascular stiffness and increases in basement membrane thickness. AGE binding to specific cell surface receptors (e.g., receptors for AGE, RAGE), particularly on macrophages and endothelial cells, stimulates activation of signaling cascades that promote inflammation and oxidative stress. For example, AGE-RAGE interaction activates the transcription factor NF-κB, leading to multiple pathologic changes in gene expression. Further, AGEs formed intracellularly alter the function of many important cellular proteins. Studies in animal models provide strong evidence that AGE formation is a key process mediating hyperglycemic damage. However, to date, studies of anti-AGE compounds (e.g., aminoguanidine) have failed to demonstrate efficacy in preventing or ameliorating diabetic complications in humans.

INCREASED POLYOL PATHWAY FLUX

Metabolism of glucose through the aldose reductase pathway is generally minor because this enzyme has a low affinity for glucose. However, in the setting of intracellular hyperglycemia (most likely to occur in tissues that cannot

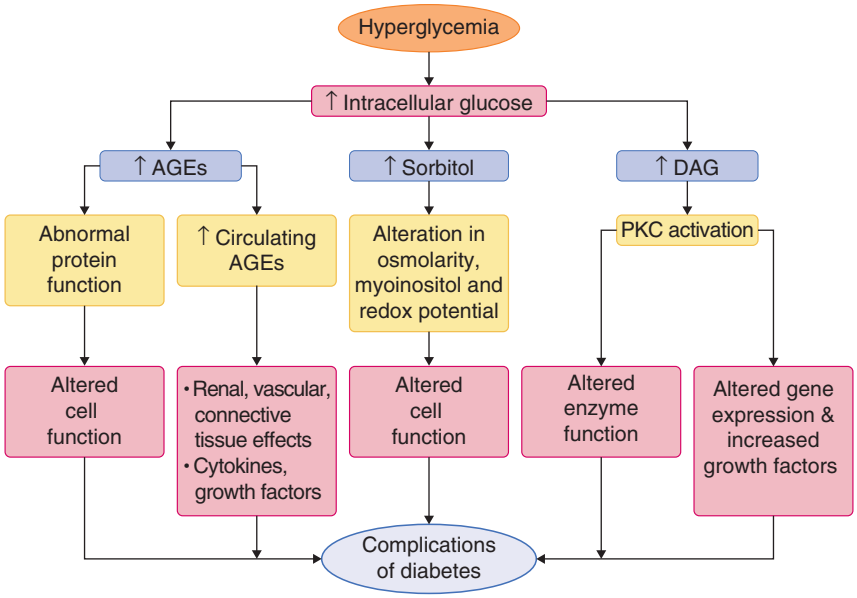

FIGURE 216-8. **Proposed mechanisms of hyperglycemia-induced vascular complications.** See text for discussion. AGEs = advanced glycation end products; DAG = diacylglycerol; PKC = protein kinase C.

downregulate glucose uptake, such as neurons and endothelial cells), there is increased flux through this pathway, leading to an accumulation of osmotically active sorbitol within the cell. Increased cellular osmolarity occurs, along with an increase in redox stress due to depletion of the reduced form of nicotinamide adenine dinucleotide phosphate and reduced glutathione. Inhibitors of aldose reductase have been proposed as a therapeutic strategy to reduce diabetic complications. Current evidence from clinical trials does not support their use, but this remains an active area of research.

ACTIVATION OF PROTEIN KINASE C

Intracellular hyperglycemia leads to increased de novo synthesis of diacylglycerol, which is a major activator of the protein kinase C family of enzymes. Activation of protein kinase C initiates a complex network of intracellular signaling that alters gene expression and results in enhanced angiogenesis, vasoconstriction, vascular permeability (by increases in vascular endothelial growth factor), cytokine activation, and extracellular matrix expansion. These alterations in cellular function have been linked to the development of microvascular complications (especially retinopathy) and atherosclerosis. Inhibitors of specific protein kinase C isoforms are being studied in clinical trials as agents specific for diabetic retinopathy and macular edema.

INCREASED HEXOSAMINE PATHWAY FLUX

In the setting of hyperglycemia and excess fatty acid oxidation, there is also increased flux of glucose through the hexosamine pathway, leading to increases in glucosamine 6-phosphate and ultimately post-translational modification of certain cytoplasmic and nuclear proteins. Associated with this are increases in expression of key genes, including those for transforming growth factor (α and β_1) and plasminogen activator inhibitor–1, and inhibition of endothelial nitric oxide synthase activity. Whereas the pathway has been linked to defective insulin action, its role in specific complications remains unclear.

These multiple and complex pathways are not mutually exclusive but are interconnected and may have a common antecedent process, which is overproduction of superoxide by the mitochondrial electron transport chain. Superoxide generates the production of other reactive oxygen species that can lead to cellular damage in a variety of ways. Data from animal models support the possibility that correction of diabetes-induced superoxide overproduction will have positive downstream effects on the various pathways leading to hyperglycemic tissue damage, but this remains to be confirmed in human studies.

Microvascular Complications

DIABETIC RETINOPATHY

Diabetic retinopathy (Chapter 395) is a highly prevalent, pathognomonic, microvascular complication, eventually affecting more than 50% of patients with long-term diabetes, although it causes vision impairment less frequently. The occurrence of vision loss due to diabetic retinopathy has declined during the past few decades as glucose and blood pressure control have improved in the population with diabetes. Nonetheless, it remains an important cause of preventable blindness, especially among patients with poor metabolic control. Both vascular and neural tissues in the retina are affected by chronic hyperglycemia. Early changes include the loss of retinal supporting cells (pericytes), basement membrane thickening, and retinal blood flow changes. Damaged retinal capillaries leak protein, red blood cells, and lipids, leading to retinal edema. Chronic retinal hypoxia (due to capillary occlusion) promotes neovascularization; these new vessels are abnormal and prone to rupture. Retinal hemorrhage, inflammation, and scarring can ultimately lead to traction retinal detachment and permanent vision loss (Table 216-13).

TABLE 216-13 CLASSIFICATION OF DIABETIC RETINOPATHY

	CLINICAL FEATURES
Mild NPDR	At least one microaneurysm
Moderate NPDR	Microaneurysms, intraretinal (blot) hemorrhage, soft exudates, venous beading, intraretinal microvascular abnormalities
Severe NPDR	More extensive intraretinal hemorrhages (>20 in each of four quadrants) *or* venous beading in at least two quadrants *or* prominent intraretinal microvascular abnormalities
PDR	Neovascularization and/or vitreous or pre-retinal hemorrhage; traction retinal detachment
Clinically significant macular edema	Retinal thickening or hard exudates approaching or involving the center of the macula

NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy.

Diabetic retinopathy can be detected by dilated funduscopy, with early signs being the presence of microaneurysms, exudates, and intraretinal hemorrhages. Additional tests, including fluorescein angiography and ocular coherence tomography, are helpful to detect abnormal vessel permeability and macular edema, which can threaten vision. Regular screening by an eye care specialist (an ophthalmologist or optometrist) is recommended for all patients with diabetes because significant and potentially vision-threatening retinopathy can be present in the absence of any symptoms.[24] Screening should begin at diabetes diagnosis for patients with type 2 diabetes because hyperglycemia has typically been present for years before it is recognized clinically. For patients with type 1 diabetes, screening can begin at 5 years after diagnosis or after puberty for childhood onset. Because retinopathy can progress rapidly during pregnancy, screening and follow-up should be more aggressive during this time (Table 216-14).

As with other diabetic complications, intensive glycemic control can prevent diabetic retinopathy, delay its progression, and reduce the long-term need for

TABLE 216-14 RECOMMENDED INTERVALS FOR DIABETIC RETINOPATHY SCREENING

DIABETES TYPE	FIRST EXAMINATION	FOLLOW-UP
Type 1	5 years after diagnosis	Annual
Type 2	At time of diagnosis	Annual
Established diabetes during pregnancy	Before or soon after conception	At least every 3 months

ocular surgery. However, it has limited effects on advanced retinal disease. Blood pressure control is also important to prevent worsening of retinopathy; there is some evidence that renin-angiotensin system (RAS) blockers may be especially beneficial.

Treatment of diabetic retinopathy (Chapter 395) includes laser photocoagulation, which can ablate abnormal vessels (thus reducing the risk of hemorrhage) and treat macular edema. Laser photocoagulation can be focal (to treat clinically significant macular edema or nonproliferative diabetic retinopathy) or panretinal (to treat severe nonproliferative diabetic retinopathy or proliferative diabetic retinopathy). Vitrectomy is a surgical procedure to remove hemorrhage and scar tissue that is obscuring vision. Nonsurgical therapies include intravitreal injection of glucocorticoids or anti–vascular endothelial growth factor monoclonal antibodies (e.g., ranibizumab) to treat macular edema. The established efficacy of retinopathy treatment, particularly photocoagulation, in preventing vision loss provides strong justification for routine retinopathy screening. There is evidence that treatment with fenofibrate reduces the progression of retinopathy, although the medication has not been approved for this indication in the United States. In addition to its well-known effects on lipid metabolism, fenofibrate appears to have significant anti-inflammatory, antiangiogenic, and antioxidant properties that are relevant to retinal disease. The presence of retinopathy is not considered a contraindication to the use of aspirin for CVD prevention.

Other eye conditions also affect patients with diabetes. Transient osmotically induced refractive error is common, especially at the time of diabetes diagnosis, but resolves with glucose control. Age-related eye conditions, such as cataracts and glaucoma, tend to occur at younger ages among diabetic patients. Diplopia and other gaze disorders due to acute mononeuropathy involving the cranial nerves (typically III or VI) are also more common in diabetes.

DIABETIC NEPHROPATHY

Diabetic nephropathy (Chapter 116) remains the most common single cause of end-stage renal failure, accounting for up to 50% of the cases in Western societies. Further, despite advances in the management of glucose and hypertension, the prevalence of chronic kidney disease among patients with diabetes has declined little, if at all, in the past several decades. Overall, 20 to 30% of type 1 and type 2 diabetic patients develop evidence of nephropathy, although fewer type 2 patients progress to end-stage renal disease (ESRD). This may be because of competing mortality from CVD, with fewer surviving to ESRD. However, because of their much greater frequency in the population, the majority of diabetes patients presenting for treatment of ESRD (dialysis or transplantation) have type 2 diabetes.[25] The major risk factor for the development of diabetic nephropathy is the duration and severity of hyperglycemia, but there is evidence for variation in genetic susceptibility. For example, African Americans and individuals with a family history of diabetic or nondiabetic renal disease are at higher risk for diabetic nephropathy. An insertion/deletion polymorphism in the gene encoding angiotensin-converting enzyme (ACE) has been widely reported to be associated with increased risk of diabetic nephropathy, but variants in genes involved in the polyol pathway, lipid metabolism, inflammatory cytokines, angiogenesis, and oxidative stress have also been identified.

Diabetic nephropathy develops during many years to decades, with a prolonged "silent" period before clinical detection, followed by more rapid progression to overt renal disease (Chapter 116). In the classic view, the hallmark of diabetic nephropathy is the development of proteinuria, which is due to alteration in glomerular basement membrane permeability and increases in intraglomerular pressure. The first clinical evidence of incipient nephropathy is the development of albuminuria, which is quantitatively minor at first (microalbuminuria, urine albumin-to-creatinine ratio of 30 to 300 mg/g) and then progresses to overt proteinuria, sometimes in the nephrotic range (>2 g/day). During the microalbuminuria phase, GFR is preserved but begins to decline in parallel with increasing proteinuria, leading to ESRD 5 to 15 years after the first detection of abnormal albumin excretion. However, recent evidence suggests that chronic kidney disease in diabetes is more heterogeneous than previously thought, with some patients progressing to advanced stages of chronic kidney disease in the absence of albuminuria (Fig. 216-9). Nonalbuminuric diabetic kidney disease appears more likely to occur in older patients with type 2 diabetes and may reflect, in part, the concurrence of multiple renal risk factors, including hypertension, obesity, and dyslipidemia. Further, microalbuminuria does not inevitably progress, with some patients regressing to normal or maintaining small but stable amounts of albuminuria. However, persistent and increasing albuminuria is a marker of high risk for progression to clinical nephropathy. Pathologic changes that are typical of diabetic nephropathy include an increase in glomerular basement membrane thickness and increased accumulation of extracellular matrix leading to mesangial expansion and the classic Kimmelstiel-Wilson nodular lesion.

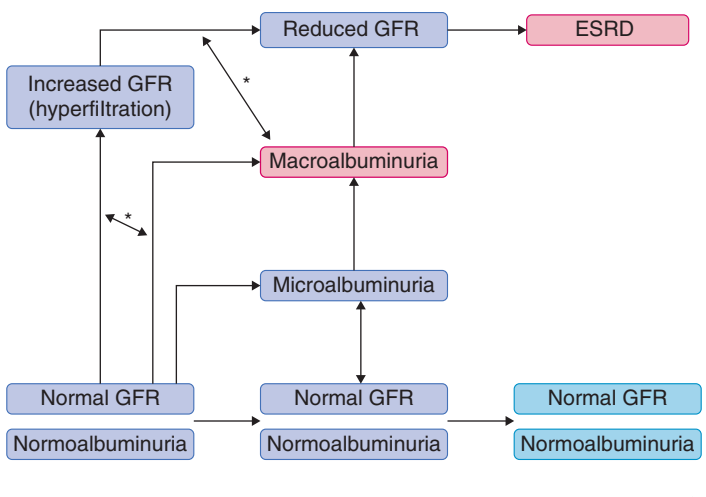

FIGURE 216-9. Development of diabetic nephropathy. See text for discussion. GFR = glomerular filtration rate; ESRD = end-stage renal disease. *GFR and albuminuria may progress independently of each other, that is, patients may have microalbuminuria or macroalbuminuria even though their GFR is normal or even slightly elevated. However, macroalbuminuria is usually associated with reduced GFR and is a strong risk for progressive ESRD. (From Boger CA, Sedor JR. GWAS of diabetic nephropathy: is the GENIE out of the bottle? *PLoS Genet*. 2012;8:e1002.)

Patients with diabetes should be screened annually for renal involvement (Chapter 116) by measurement of albumin on a spot urine sample with a sensitive immunoassay to detect microalbuminuria and by measurement of serum creatinine for calculation of estimated GFR. The finding of moderately increased urine albumin-to-creatinine ratio (30 to 300 mg albumin per gram of creatinine) should be confirmed on two of three repeated tests because transient increases are not uncommon but may not be clinically important. Data from the DCCT and other studies provide strong evidence that aggressive glycemic control can prevent the development of diabetic nephropathy and can retard the progression of microalbuminuria. However, there is little evidence that glycemic control can modulate the course once clinical albuminuria (>300 mg/day) and declining GFR occur. Central to the treatment of patients with albuminuria (micro or clinical) is intensive blood pressure control, preferentially by blockade of the RAS. Both ACE inhibitors and angiotensin receptor blockers have been shown to delay the progression of diabetic nephropathy and are recommended for patients with albuminuria even in the absence of hypertension. Despite initial enthusiasm, combined ACE inhibitor and angiotensin receptor blocker therapy is not recommended because of high rates of hyperkalemia and acute renal injury. In hypertensive patients, other drugs, such as calcium-channel blockers, diuretics, and β-blockers, can be used as additional therapy if needed to achieve adequate blood pressure control. There is little evidence to support use of RAS blockade in diabetic patients who are normotensive and normoalbuminuric, although there may be a therapeutic rationale for use of these agents in patients who cannot achieve adequate glycemic control. Dietary protein restriction has been recommended in the past for patients with nephropathy, but recent trials have been unable to demonstrate an effect of a low-protein diet on the rate of deterioration of GFR.

DIABETIC NEUROPATHY

Diabetic neuropathy (Chapter 392) is a common complication of diabetes, with an estimated lifetime prevalence of about 50%. Diabetic neuropathy can be manifested in a variety of syndromes, including radiculoplexopathy and autonomic neuropathy, but the most common form is a characteristic distal symmetrical polyneuropathy (DSP).[26] Despite its high prevalence, there is no distinct neuropathic symptom or lesion that is specific to diabetes, and separation of diabetic neuropathy from other causes can be problematic. As for other microvascular complications, the etiology of DSP is attributed to hyperglycemia, as demonstrated by the dramatic 60% reduction in neuropathy in the intensive treatment group in the DCCT study. However, the possibility that the pathogenesis of DSP may differ in type 2 diabetes, with dyslipidemia and insulin resistance also contributing, has recently emerged. Support for this view comes from largely negative neuropathy results of clinical trials of intensive glucose control in type 2 diabetes (e.g., Action to Control Cardiovascular Risk in Diabetes [ACCORD] trial, VA Cooperative study) and the observation that the prevalence of DSP is already increased in the setting of pre-diabetes and the metabolic syndrome.

The clinical manifestations of DSP include symptoms of pain, paresthesias, and numbness that typically begin in the feet and progress more proximally in a "stocking and glove" distribution (Chapter 392). Loss of sensation, which may not be noticed by the patient, constitutes an important risk factor for falls due to gait instability. Ulceration, uncontrolled infection, and amputation can also occur from altered foot mechanics and inability to perceive repetitive trauma or other foot injury. For some patients, neuropathic pain can be severe and disabling, resulting in a major reduction in quality of life. DSP can be diagnosed by the presence of classic symptoms and by loss of ability to perceive pressure from a nylon (Semmes-Weinstein) monofilament, impaired vibration sense or loss of pinprick sensation. Additional tests, such as nerve conduction studies or electromyography, are occasionally indicated to distinguish DSP from radiculopathy. Current treatment options are mostly limited to control of metabolic risk factors (i.e., glucose, lipids) and symptoms. The chronic pain of DSP can be difficult to manage. Available therapies include tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and anticonvulsants (such as gabapentin and pregabalin); opioids are not specifically useful and their use has major addiction potential.

Other forms of diabetic nerve damage (Chapter 392) include small-fiber predominant neuropathy, radiculoplexopathy (diabetic amyotrophy), noncompressive radiculopathy, and mononeuritis multiplex. Autonomic neuropathy can be manifested as gastroparesis, urinary retention, erectile dysfunction, sudomotor dysfunction (typically anhidrosis of the extremities with or without hyperhidrosis of the trunk), cardiac arrhythmias, and disturbance of gut motility (diabetic diarrhea or constipation). Cardiac autonomic neuropathy is an especially ominous form of diabetic autonomic neuropathy. Typical clinical manifestations of cardiac autonomic neuropathy include resting tachycardia, diminished heart rate variability, and orthostatic blood pressure changes. Patients with cardiac autonomic neuropathy are at high risk for myocardial infarction, congestive heart failure, and sudden cardiac death.

DIABETIC FOOT

The combination of sensory impairment due to peripheral neuropathy and reduced tissue perfusion due to large-vessel atherosclerosis (peripheral arterial disease) or microvascular dysfunction can result in ulceration, infection, and ultimately lower extremity amputation. A typical case involves development of an ulceration (often surrounded by callus formation) on the plantar surface of the foot, often underneath the metatarsal heads.[27] Ulceration can be slow to heal because of repetitive trauma from walking and impaired blood flow; hyperglycemia may also impair wound healing by effects on white blood cell migration and function. In the absence of protective sensation, an infection may fester for weeks and eventually invade the bone, leading to osteomyelitis. Altered foot mechanics can also lead to repeated (and usually undetected) fractures that destroy normal foot architecture and result in the classic Charcot foot deformity.

For many patients, foot amputation is the most feared diabetic complication; fortunately, it can be prevented in most cases but requires vigilance on the part of the patient and health care team. Routine foot examination, especially for patients who have evidence of sensory loss, should be performed at every medical visit, and patients should be instructed to inspect their feet daily for cracks, fissures, ulcers, or inflammation. Patients should avoid walking barefoot (even at home) and should wear protective covering (avoid sandals) outside. Thermal injuries can be prevented by avoiding use of heating pads or hot-water bottles on the feet. Referral to a foot care specialist should be considered for patients with sensory loss, foot deformity, extensive callus formation, and nonhealing ulcers. Ulcers are treated with aggressive débridement of necrotic tissue and systemic antibiotics (guided by culture of infected tissue) if infection is present. Pressure "off-loading" by use of special shoes, orthotics, or application of total contact casts may be necessary to allow healing. Additional treatments include use of topical platelet-derived growth factor, bioengineered skin substitutes, hyperbaric oxygen, and negative-pressure wound therapy, although none of these has shown conclusive evidence of effectiveness in promoting wound healing.

Other Associated Conditions

Patients with diabetes can develop a number of electrolyte and acid-base abnormalities,[28] even in the absence of ketoacidosis or hyperosmolarity. In type 4 renal tubular acidosis (Chapter 110), for example, hyperkalemia can require dietary and medical interventions.

Although not traditionally recognized as diabetic complications, there are a number of disorders that are increased in frequency or severity in patients with diabetes and that have a plausible or established relationship with hyperglycemia. These include periodontal disease, Alzheimer dementia, and musculoskeletal disorders, such as limited joint mobility, adhesive capsulitis, Dupuytren contracture, and trigger finger (flexor tenosynovitis). Patients with poorly controlled diabetes are widely thought to have increased susceptibility to infection, particularly with fungal pathogens. Defects in immune function (impaired neutrophil chemotaxis) have been described in diabetes, but whether this occurs in reasonably controlled diabetes or contributes to clinical infection is unclear. The incidence of osteoporotic fractures appears to be increased in women with diabetes, despite the presence of normal or even increased bone density. There is also emerging evidence that the frequency of some cancers (e.g., pancreatic, endometrial, colorectal, breast) is increased among people with diabetes.

CARDIOVASCULAR DISEASE IN DIABETES

Atherosclerotic CVD is the major cause of morbidity and mortality for patients with diabetes and contributes substantially to its economic costs. The clinical and pathologic features of CVD in diabetes are generally not distinguishable from those occurring in nondiabetic individuals, but they are manifested at an earlier age, are more aggressive, and are associated with mortality rates that are two to four times higher in patients with diabetes (Chapter 46). This increased CVD risk is true for both type 1 and type 2 diabetes, with CVD in type 1 diabetes being strongly associated with concurrent presence of renal disease. Diabetes is also an important risk factor for peripheral vascular disease and stroke, which carries greater mortality risk than in nondiabetic patients.

Pathobiology of Cardiovascular Disease in Diabetes

The pathogenesis of atherosclerotic CVD in diabetes is complex and multifactorial, with several mechanisms playing key roles. *Metabolic factors*, including hyperglycemia, insulin resistance, dyslipidemia, and increases in circulating free fatty acids, contribute to atherosclerotic plaque formation. Increases in *oxidation and glycoxidation* of lipoproteins increase their atherogenicity and enhance foam cell formation. *Endothelial dysfunction*, an early event in the development of atherosclerosis, has been described in association with several metabolic syndrome components, including hyperglycemia, insulin resistance, hypertension, and dyslipidemia. Systemic *inflammation*, which contributes to accelerated plaque formation, is increased in diabetes and obesity as a consequence of increased cytokine production by adipose tissue. Finally, diabetes is characterized by a *prothrombotic* state due to enhanced platelet reactivity and alterations in coagulation factors, including increased circulating levels of fibrinogen and plasminogen activator inhibitor–1.

Diabetic Cardiomyopathy and Heart Failure

Diabetic cardiomyopathy is defined as alterations in cardiac structure and function that are not directly attributable to coronary artery disease or hypertension (Chapters 52 and 53). Characteristic features include cardiac hypertrophy, left ventricular dysfunction (diastolic may precede systolic), and altered myocardial metabolism. Diabetes is a recognized risk factor for the development of heart failure, even in the absence of atherosclerotic heart disease. For example, in the Framingham Heart Study, the frequency of heart failure was twice in diabetic men and five times in diabetic women compared with age-matched controls and persisted despite correction for hypertension, obesity, dyslipidemia, and coronary artery disease. Increased activation of the renin-angiotensin-aldosterone system and formation of AGEs are thought to contribute to

myocardial fibrosis and stiffness, and altered substrate utilization (preferential use of free fatty acids) can promote myocyte dysfunction by enhanced production of reactive oxygen species and other mechanisms. Characteristic changes in myocardial function and structure were reported in type 1 diabetes in the DCCT and Epidemiology of Diabetes Interventions and Complications (EDIC) study and were related to long-term glycemic control.

Prevention of Cardiovascular Disease in Diabetes

Aggressive control of CVD risk factors is recommended for most patients with diabetes, keeping in mind that the presence of diabetes is considered the risk equivalent of a prior myocardial infarction by most risk assessment algorithms (e.g., Framingham risk score, Adult Treatment Panel III Report of the National Cholesterol Education Program). Assessment of blood pressure, lipid profile, and smoking status should be included as part of routine diabetes care. Determination of the optimal targets for risk factor control has been the subject of several large randomized trials, which have informed consensus guidelines.

GLUCOSE CONTROL

Hyperglycemia is a major risk for atherosclerotic CVD. In population-based studies including diabetic and nondiabetic cohorts, HbA_{1c} has been reported as an independent predictor of all-cause and CVD mortality, and among individuals with diabetes, every 1% rise in HbA_{1c} is associated with a 30% increase in all-cause mortality and a 40% increase in CVD mortality. Compelling evidence for the benefit of intensive glucose control in patients with type 1 diabetes was shown in the DCCT/EDIC study, in which CVD events were reduced by 58%. However, in type 2 diabetes, hyperglycemia occurs in the setting of multiple other CVD risk factors, including hypertension, dyslipidemia, and obesity, which also contribute to risk, so the contribution of glucose control is less clear. Several large clinical trials in patients with type 2 diabetes have failed to show that aggressive control of hyperglycemia has important effects on CVD outcomes (see later), highlighting the complex pathogenesis of vascular disease in diabetes. Similarly, an intensive lifestyle program designed to achieve weight loss and exercise goals also failed to demonstrate significant effects on CVD outcomes in type 2 diabetes patients.

The strongest evidence in favor of intensive glucose control comes from the long-term follow-up of the UKPDS, which demonstrated 15% reduction in myocardial infarction and 13% reduction in all-cause mortality in the intensive versus conventional treatment group. More recently, in the ACCORD trial, an intensive treatment arm, designed to maintain HbA_{1c} below 6%, was compared with conventional treatment with HbA_{1c} goal of 7.5% in a cohort of type 2 diabetes patients at high risk for CVD. This trial was stopped early because of unexpected increased mortality, largely CVD related, in the intensive treatment group. The reasons for increased mortality with intensive treatment are not known for certain, but increased frequency and severity of hypoglycemia or the toxicity of specific drugs or combinations has been proposed. Secondary analysis of ACCORD data showed a reduction in nonfatal myocardial infarction in the intensive treatment group, leading to speculation that some patients might still benefit. Other studies designed to address this, including the VA Cooperative Study and ADVANCE, also failed to show CVD benefit for intensive glucose control. These trials differed somewhat in patient characteristics, HbA_{1c} goal, and specific treatment regimens, and the largely negative results stimulated controversy. However, some consensus views have emerged[29]: (1) in the current era of effective treatment of other CVD risk factors (i.e., with statins, RAS blockers, antiplatelet therapy), the additional benefits of intensive glycemic control are modest at best; (2) patients with long-standing diabetes or established CVD are least likely to benefit from intensive glucose lowering; (3) the benefits of glucose lowering in the prevention of microvascular complications provide an independent rationale for strict glucose control for many patients; and (4) specific glycemic targets should be individualized according to the patient's characteristics (e.g., comorbidities, life expectancy, hypoglycemia risk) and preferences.

HYPERTENSION

Hypertension (Chapter 70) is a common comorbidity in diabetes, affecting the majority of patients with type 2 diabetes, and constitutes an important modifiable CVD risk factor. Further, in even the earliest stages of diabetic nephropathy (i.e., microalbuminuria), hypertension is further accelerated. In type 1 diabetes, hypertension is generally the result of concurrent renal disease, with both contributing to CVD risk. The importance of blood pressure control in reducing CVD events as well as microvascular outcomes in patients with diabetes was established by several major trials, including the UKPDS, Systolic Hypertension in the Elderly Program (SHEP), Hypertension Optimal Treatment (HOT) study, and others. However, analysis of these and other trials failed to show evidence of improved outcomes (i.e., in myocardial infarction or mortality) with systolic blood pressure targets of 130 mm Hg or lower. An even more aggressive target systolic blood pressure of less than 120 mm Hg was shown to be of no additional benefit in reducing CVD events in the ACCORD trial. Current guidelines from the American Heart Association and the American College of Cardiology recommend a blood pressure goal of less than 130/80 for most patients, including those with diabetes. Other guidelines, including those from the American Diabetes Association (ADA), suggest a blood pressure target of less than 140/90 mm Hg for patients with diabetes but with the further recommendation that a lower target may be considered for selected patients if it can be achieved without excessive treatment burden. However, many of these recommendations are based on expert opinion rather than on evidence from randomized trials, and some uncertainty remains.

The choice of antihypertensive agent has also received considerable study, which is complicated by the fact that many patients will require treatment with two or more drugs to achieve target blood pressure. ACE inhibitors and angiotensin receptor blockers are generally considered first-line therapy for patients with diabetes, in part on the basis of their demonstrated renoprotective benefits. In addition, results from several randomized trials, including the Heart Outcomes Protection Study (HOPE), Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET), and Appropriate Blood Pressure Control in Diabetes (ABCD), indicated improved cardiovascular outcomes with ACE inhibitors compared with other antihypertensive drugs, although this was not the case for the UKPDS, in which β-blockers were equally effective. Calcium-channel blockers and low-dose diuretics are also recommended as add-on therapy if needed to achieve blood pressure targets. Use of β-blockers should be considered in the setting of established CVD because of their proven benefits in patients with prior myocardial infarction and congestive heart failure. However, β-blockers should be used with caution in patients at high risk for hypoglycemia because they may blunt the autonomic warning symptoms associated with low glucose concentration. Both β-blockers and thiazide diuretics have been reported to increase the risk for development of diabetes, although there is little evidence for significant deterioration of glycemic control in patients with diabetes.

DYSLIPIDEMIA

The characteristic dyslipidemia of type 2 diabetes and insulin-resistant states, which includes low levels of high-density lipoprotein (HDL) cholesterol, elevated triglycerides, and small dense low-density lipoprotein (LDL) particles, is highly atherogenic (Chapter 195). LDLs also are prone to oxidative modification in the setting of hyperglycemia, which enhances their atherogenicity. There is substantial clinical trial evidence to support lowering of LDL cholesterol levels with statin drugs in the majority of patients with diabetes older than 40 years. These findings come from trials limited to diabetes (Collaborative Atorvastatin Diabetes Study [CARDS]) and to diabetes subset analysis of larger trials (Heart Protection Study), all of which report similar CVD benefits of statin therapy among diabetics and nondiabetics. ADA recommendations are for target LDL levels of less than 100 mg/dL for most adult patients with diabetes and less than 70 mg/dL for diabetic patients with established CVD or multiple risk factors. Recent guidelines from the American Heart Association (AHA) and American College of Cardiology (ACC) have focused on CVD risk stratification to determine the need for and intensity of statin therapy. With this approach, virtually all patients with diabetes (aged 40 to 75 years) would be candidates for statin therapy, regardless of baseline level of LDL cholesterol. Diabetic patients with established atherosclerotic CVD or estimated 10-year CVD risk of more than 7.5% would receive high-intensity statin treatment (regimens sufficient to lower LDL cholesterol >50% from untreated baseline); all others would be considered for moderate-intensity treatment (lowering of LDL cholesterol 30 to <50%). The evidence base to support these new recommendations is considered relatively strong. Although the ADA and the AHA/ACC guidelines differ in structure, ultimately the recommendations for most patients with diabetes will be similar with either approach.

Recent observations from several trials (e.g., JUPITER) and observational cohort studies of an increase in incident diabetes with statin therapy have generated concern, although the risk appears to be small in magnitude (hazard ratio, ≈1.2) and is outweighed by the substantial benefits of CVD protection.[30] Clinically relevant effects of statins on glucose control among established diabetics have not been reported. In patients intolerant of statins, nicotinic acid (niacin) can be used, although CVD outcome trials have been disappointing

despite substantial improvement in lipid parameters, including lowering of LDL cholesterol and increasing of HDL cholesterol levels. Further, nicotinic acid may worsen insulin resistance and glycemic control in some patients. Bile acid sequestrants, such as colesevelam or cholestyramine, can also be used but may exacerbate the hypertriglyceridemia characteristic of diabetic dyslipidemia.

In contrast to the definitive benefits of LDL lowering, there is less evidence that pharmacologic treatment of hypertriglyceridemia or of low HDL cholesterol levels reduces CVD risk. This may be in part due to the lesser efficacy of available drugs to alter these lipid subfractions. Trials with fibrate derivatives (gemfibrozil and fenofibrate) have yielded mixed results, and the addition of fenofibrate to a statin did not reduce the rate of major CVD events compared with statin alone in the ACCORD trial. Because most statins have some triglyceride-lowering effect, maximizing statin dose should be considered for patients with high triglyceride levels. Lifestyle factors are also effective, including weight loss and dietary modification (reduced fat diet, avoidance of alcohol). Omega-3 fatty acid supplementation can lower triglyceride levels but is not effective for the routine primary prevention of cardiovascular events in diabetic patients. Pharmacologic treatment (i.e., with fibrates or fish oil supplements) of severe hypertriglyceridemia (triglyceride level >1000 mg/dL) is indicated to prevent acute pancreatitis.

ANTIPLATELET THERAPY

Prophylactic low-dose aspirin therapy is widely used for prevention of cardiovascular events in high-risk patients (i.e., those with prior myocardial infarction or stroke), with reported risk reductions of about 12%. In patients with diabetes, aspirin is not effective for the primary prevention of cardiovascular disease and increases bleeding events. Current guidelines recommend aspirin therapy for diabetic patients with a prior CVD event (secondary prevention), but it is uncertain whether primary prevention is beneficial even in higher risk patients, because the potential adverse effects from bleeding may outweigh the potential benefits. The optimal dose (balancing thrombosis prevention with the risk of bleeding) of aspirin has not been established and may differ according to patient characteristics, but 75 to 162 mg/day is commonly recommended. For high-risk patients who are unable to tolerate aspirin, clopidogrel is an effective alternative.

TREATMENT OF ESTABLISHED CARDIOVASCULAR DISEASE IN DIABETES

Rx

In general, treatment of clinically established CVD, including acute coronary syndromes and stable angina, is similar in diabetic and nondiabetic patients. There is some evidence that ischemic symptoms may be less intense, atypical, or absent in diabetic patients, leading to higher rates of "silent" myocardial infarction. However, a strategy of screening for ischemic heart disease, by exercise stress testing, in asymptomatic patients did not result in lower event rates or improved outcomes. Therefore current recommendations are for coronary artery disease screening in patients with symptoms suggestive of ischemia.

The role of intravenous insulin (with or without potassium and glucose infusion) in the setting of acute myocardial infarction has been considered in a few studies. In the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, acute myocardial infarction patients with diabetes were treated with standard therapy or with insulin infusion during the first 48 hours, followed by continued insulin use after hospital discharge. Mortality after 1 year was reduced by 30% in the insulin-treated group. However, the implications of these results have been debated because factors other than insulin treatment differed between the two groups (i.e., sulfonylureas were routinely used in the standard therapy group but withdrawn from the insulin group). These findings subsequently were not confirmed in a follow-up study, and this approach has largely been abandoned.

Several studies have addressed the roles of medical therapy and revascularization in diabetic patients with coronary artery disease. Among them, the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study demonstrated that a policy of medical management (including aggressive risk factor modification) was as effective as early revascularization in diabetic patients with stable angina. In the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, diabetic patients with multivessel coronary disease had better outcome (reduced rates of death from any cause or nonfatal myocardial infarction) with coronary bypass surgery compared with percutaneous intervention with drug-eluting stents, although strokes were more frequent in the surgical group.

Grade A References

A1. Misso ML, Egberts KJ, Page M, et al. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. *Cochrane Database Syst Rev*. 2010;1:CD005103.
A2. Tauschmann M, Thabit H, Bally L, et al. Closed-loop insulin delivery in suboptimally controlled type 1 diabetes: a multicentre, 12-week randomised trial. *Lancet*. 2018;392:1321-1329.
A3. Beck RW, Riddlesworth T, Ruedy K, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections. The DIAMOND randomized clinical trial. *JAMA*. 2017;317:371-378.
A4. Lind M, Polonsky W, Hirsch IB, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: the GOLD randomized clinical trial. *JAMA*. 2017;317:379-387.
A5. The Type 1 Diabetes TrialNet Oral Insulin Study Group. Effect of oral insulin on prevention of diabetes in relatives of patients with type 1 diabetes. A randomized clinical trial. *JAMA*. 2017;318:1891-1902.
A6. Senat MV, Affres H, Letourneau A, et al. Effect of glyburide vs subcutaneous insulin on perinatal complications among women with gestational diabetes: a randomized clinical trial. *JAMA*. 2018;319:1773-1780.
A7. Hemmingsen B, Lunc S, Gluud C, et al. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2013;11:CD008143.
A8. Hayward RA, Reaven PD, Wiitala WL, et al. Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;372:2197-2206.
A9. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. *N Engl J Med*. 2017;376:641-651.
A10. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet*. 2015;386:964-973.
A11. Eng C, Kramer CK, Zinman B, et al. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. *Lancet*. 2014;384:2228-2234.
A12. Davies MJ, Bergenstal R, Bode B, et al. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. *JAMA*. 2015;314:687-699.
A13. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375:311-322.
A14. Mann JFE, Ørsted DD, Brown-Frandsen K, et al. Liraglutide and renal outcomes in type 2 diabetes. *N Engl J Med*. 2017;377:839-848.
A15. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834-1844.
A16. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373:232-242.
A17. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117-2128.
A18. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377:644-657.
A19. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med*. 2019;380:2295-2306.
A20. Reznik Y, Cohen O, Aronson R, et al. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomised open-label controlled trial. *Lancet*. 2014;384:1265-1272.
A21. Finfer S, Liu B, Chittock DR, et al. The NICE-SUGAR Study Investigators. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med*. 2012;367:1108-1118.
A22. Lean ME, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet*. 2018;391:541-551.
A23. Bohula EA, Scirica BM, Inzucchi SE, et al. Effect of lorcaserin on prevention and remission of type 2 diabetes in overweight and obese patients (CAMELLIA-TIMI 61): a randomised, placebo-controlled trial. *Lancet*. 2018;392:2269-2279.
A24. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol*. 2015;3:866-875.
A25. Aiello LP, Sun W, Das A, et al. Intensive diabetes therapy and ocular surgery in type 1 diabetes. *N Engl J Med*. 2015;372:1722-1733.
A26. Nguyen Q, Brown D, Marcus D, et al. Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE. *Ophthalmology*. 2012;119:789-801.
A27. Fried L, Emanuele N, Zhang J, et al. Combined angiotensin inhibition for the treatment of diabetic nephropathy. *N Engl J Med*. 2013;369:1892-1903.
A28. Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369:145-154.
A29. Zoungas S, Chalmers J, Neal B, et al. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. *N Engl J Med*. 2014;371:1392-1406.
A30. Emdin CA, Rahimi K, Neal B, et al. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2015;313:603-615.
A31. Brunström M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ*. 2016;352:1-10.
A32. Bowman L, Mafham M, Wallendszus K, et al. Effects of n-3 fatty acid supplements in diabetes mellitus. *N Engl J Med*. 2018;379:1540-1550.
A33. Bowman L, Mafham M, Wallendszus K, et al. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med*. 2018;379:1529-1539.

GENERAL REFERENCES

For the General References and other additional features, please visit Expert Consult at https://expertconsult.inkling.com.

GENERAL REFERENCES

1. DiMeglio LA, Evans-Molina C, Oram RA. Type 1 diabetes. *Lancet*. 2018;391:2449-2462.
2. Mayer-Davis EJ, Lawrence JM, Dabelea D, et al. Incidence trends of type 1 and type 2 diabetes among youth, 2002-2012. *N Engl J Med*. 2017;376:1419-1429.
3. Husebye ES, Anderson MS, Kämpe O. Autoimmune polyendocrine syndromes. *N Engl J Med*. 2018;378:1132-1141.
4. Johnson MB, Cerosaletti K, Flanagan SE, et al. Genetic mechanisms highlight shared pathways for the pathogenesis of polygenic type 1 diabetes and monogenic autoimmune diabetes. *Curr Diab Rep*. 2019;19:1-9.
5. Langenberg C, Lotta LA. Genomic insights into the causes of type 2 diabetes. *Lancet*. 2018;391:2463-2474.
6. Nathan DM. Diabetes: advances in diagnosis and treatment. *JAMA*. 2015;314:1052-1062.
7. Karges B, Schwandt MS, Heidtmann B, et al. Association of insulin pump therapy vs. insulin injection therapy with severe hypoglycaemia, ketoacidosis and glycemic control among children, adolescents and young adults with type 1 diabetes. *JAMA*. 2017;318:1358-1366.
8. Simmons K, Gottlieb P, Michels A. Immune intervention and preservation of pancreatic beta cell function in type 1 diabetes. *Curr Diab Rep*. 2016;16:1-11.
9. Rawshani A, Rawshani A, Franzen S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med*. 2017;376:1407-1418.
10. Rawshani A, Sattar N, Franzen S, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *Lancet*. 2018;392:477-486.
11. Gregg EW, Cheng YJ, Srinivasan M, et al. Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: an epidemiological analysis of linked national survey and vital statistics data. *Lancet*. 2018;391:2430-2440.
12. Misra A, Gopalan H, Jayawardena R, et al. Diabetes in developing countries. *J Diabetes*. 2019. [Epub ahead of print.]
13. Centers for Disease Control and Prevention. National Diabetes Statistics Report, https://www.cdc.gov/diabetes/data/statistics/statistics-report.html. Accessed April 30, 2019.
14. Xu G, Liu B, Sun Y, et al. Prevalence of diagnosed type 1 and type 2 diabetes among US adults in 2016 and 2017: population based study. *BMJ*. 2018;362:1-7.
15. Morris AP. Progress in defining the genetic contribution to type 2 diabetes susceptibility. *Curr Opin Genet Dev*. 2018;50:41-51.
16. Reddon H, Patel Y, Turcotte M, et al. Revisiting the evolutionary origins of obesity: lazy versus peppy-thrifty genotype hypothesis. *Obes Rev*. 2018;19:1525-1543.
17. Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2018;319:1580-1591.
18. American Diabetes Association. Prevention or delay of type 2 diabetes: standards of medical care in diabetes—2018. *Diabetes Care*. 2018;41(suppl 1):S51-S54.
19. Selph S, Dana T, Blazina I, et al. Screening for type 2 diabetes mellitus: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2015;162:765-776.
20. Siu AL. Screening for abnormal blood glucose and type 2 diabetes mellitus: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2015;163:861-868.
21. Chamberlain JJ, Kalyani RR, Leal S, et al. Treatment of type 1 diabetes: synopsis of the 2017 American Diabetes Association standards of medical care in diabetes. *Ann Intern Med*. 2017;167:493-498.
22. Kamel KS, Halperin ML. Acid-base problems in diabetic ketoacidosis. *N Engl J Med*. 2015;372:546-554.
23. Fayfman M, Pasquel FJ, Umpierrez GE. Management of hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. *Med Clin North Am*. 2017;101:587-606.
24. DCCT/EDIC Research Group, Nathan DM, Bebu I, et al. Frequency of evidence-based screening for retinopathy in type 1 diabetes. *N Engl J Med*. 2017;376:1507-1516.
25. Anders HJ, Huber TB, Isermann B, et al. CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. *Nat Rev Nephrol*. 2018;14:361-377.
26. Vinik AI. Clinical practice. Diabetic sensory and motor neuropathy. *N Engl J Med*. 2016;374:1455-1464.
27. Armstrong DG, Boulton AJM, Bus SA. Diabetic foot ulcers and their recurrence. *N Engl J Med*. 2017;376:2367-2375.
28. Palmer BF, Clegg DJ. Electrolyte and acid-base disturbances in patients with diabetes mellitus. *N Engl J Med*. 2015;373:548-559.
29. Chamberlain JJ, Johnson EL, Leal S, et al. Cardiovascular disease and risk management: review of the American Diabetes Association standards of medical care in diabetes 2018. *Ann Intern Med*. 2018;168:640-650.
30. Chrysant SG. New onset diabetes mellitus induced by statins: current evidence. *Postgrad Med*. 2017;129:430-435.

REVIEW QUESTIONS

1. A 51-year-old man has a history of type 2 diabetes mellitus for 6 years. Past medical history is significant for chronic hepatitis C infection, chronic kidney disease stage 3, and a recent hospitalization for an upper gastrointestinal bleed. He takes a sulfonylurea for blood glucose control and rarely checks his blood glucose level. Fasting plasma glucose concentration in the office is 195 mg/dL, and his HbA_{1c} is 6.8%. What do you conclude about his glucose control?

A. His average blood glucose concentration during the past 3 months is approximately 140 mg/dL.
B. HbA_{1c} may be falsely high because of chronic kidney disease.
C. HbA_{1c} may be falsely low because of liver disease.
D. HbA_{1c} levels are increased after acute blood loss.
E. HbA_{1c} levels are more reflective of postprandial than of fasting glucose concentration.

Answer: C This patient has several reasons that his HbA_{1c} may not accurately reflect his mean plasma glucose concentration. HbA_{1c} results may be influenced by a number of factors, including conditions that alter red cell survival or cause interference with a specific assay. The HbA_{1c} may be falsely low in this patient because of cirrhosis (increased red cell turnover), recovery from recent acute blood loss (greater percentage of younger erythrocytes with shorter exposure to glucose), or transfusion (dilution of patient's blood with nondiabetic donor blood). In these instances, measurement of glycated serum proteins (fructosamine) or direct measurement of plasma glucose concentration will more accurately reflect glycemic control.

Additional information about HbA_{1c} assay methodology and interpretation of results can be obtained from the National Glycohemoglobin Standardization Program: http://www.ngsp.org.

2. A 38-year-old woman has had type 1 diabetes mellitus since the age of 12 years. She has maintained excellent control (HbA_{1c} 6.0%) with a basal/bolus injection regimen. She tests her glucose level four or five times a day, and review of her meter download shows many glucose levels in the 30s and 40s. However, the patient is unconcerned because she has no symptoms at these times. On questioning, she admits to recently "spacing out" while driving, which led to a minor traffic accident. Regarding the etiology and treatment of hypoglycemia in this patient:

A. She has adapted to low blood glucose concentration and no change in treatment is required.
B. She has developed hypoglycemia unawareness and her target HbA_{1c} should be increased.
C. Strict avoidance of hypoglycemia is of little benefit in reversing hypoglycemia-associated autonomic failure.
D. An excessive counter-regulatory hormone response to hypoglycemia may contribute to her lack of symptoms.
E. Treatment with β-blocker should be considered.

Answer: B In patients with long-standing diabetes, the counter-regulatory systems that normally would counteract the decline of glucose to dangerous levels may be impaired. This is especially true for patients with type 1 diabetes, who often have defects in glucagon and epinephrine response during hypoglycemia. This decrease in epinephrine response during hypoglycemia is accompanied by an attenuated autonomic neural response, which results in the clinical syndrome of *impaired awareness of hypoglycemia*. Without autonomic symptoms, mild hypoglycemia may proceed unnoticed to more advanced and dangerous phases. There is, however, evidence that hypoglycemia-associated autonomic failure can be reversed by strict avoidance of hypoglycemia, which can be facilitated by increasing target glucose levels.

Reno CM, Litvin M, Clark AL, Fisher SJ. Defective counterregulation and hypoglycemia unawareness in diabetes: mechanisms and emerging treatments. *Endocrinol Metab Clin North Am*. 2013;42:15-38.

3. A mother brings her 19-year-old son, who has type 1 diabetes and uses an insulin pump, to see you and to ask for referral to a dietitian. She complains that her son refuses to follow his "diabetic diet" and frequently eats junk food, including fast food (burgers, fries, pizza) and ice cream. She also worries that he sometimes skips meals, saying he is not hungry. His body mass index is 22, and his recent laboratory results show an HbA_{1c} of 7.8%, low-density lipoprotein cholesterol of 95, and normal triglycerides. Which of the following dietary recommendations is most appropriate for this patient?

A. An 1800-calorie/day American Diabetes Association diet
B. A low-carbohydrate diet
C. A low-protein diet
D. A low-fat, high-fiber diet
E. A flexible "heart healthy" meal plan that limits concentrated sweets and emphasizes fruits and vegetables

Answer: E Dietary recommendations for patients with diabetes have changed substantially over time, from the extremely low-carbohydrate, high-fat diets used before the discovery of insulin as a therapy, to "exchange diets," to more flexible meal plans. For patients with type 1 diabetes, the key element is for the patient to learn to match mealtime insulin doses to the carbohydrate content of the meal. Severely restricted diets (very low carbohydrate or low calorie) are neither required nor advisable, although avoidance of large carbohydrate loads will help minimize postmeal glycemic excursions. For most patients with type 2 diabetes who are typically overweight or obese, moderate carbohydrate intake and reduction in total calories are advised. Current recommendations allow a variety of eating styles and ethnic food preferences, with emphasis on fruits and vegetables, low-fat protein sources, and use of monounsaturated or polyunsaturated fats.

Evert A, Boucher J, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 2013;36:3821-3842.

Lasa A, Miranda J, Bullo M, et al. Comparative effect of two Mediterranean diets versus a low-fat diet on glycaemic control in individuals with type 2 diabetes. *Eur J Clin Nutr*. 2014;68:767-772.

4. A 54-year-old woman presents to her physician for treatment of hypertension. She had gestational diabetes during her last pregnancy 15 years ago, and there is a family history of type 2 diabetes (mother and older brother). Her body mass index is 36. Fasting glucose concentration is 110 mg/dL, and HbA_{1c} is 6.2%. Which of the following have been shown to reduce the progression to diabetes in high-risk patients?

A. Weight loss by reduced calorie diet
B. Treatment with metformin
C. Treatment with acarbose
D. Bariatric surgery
E. All of the above

Answer: E This patient has multiple risk factors for the development of type 2 diabetes, including family history, prior history of gestational diabetes, obesity, and hypertension. In addition, her glucose and HbA_{1c} levels are already elevated above normal, in the defined "pre-diabetes" range. All of the treatments listed have been shown to prevent or to delay the onset of diabetes in randomized clinical trials. The most consistent evidence comes from weight loss trials. Both the Finnish Diabetes Prevention Study and the U.S. Diabetes Prevention Program reported 58% reduction in diabetes with a hypocalorie, reduced fat diet combined with moderate-intensity physical activity. Weight loss achieved with bariatric surgery is also highly effective in preventing (or even reversing) diabetes. Medications, including metformin, the α-glucosidase inhibitor acarbose, and troglitazone (a thiazolidinedione), have also been shown to reduce diabetes in high-risk patients, although somewhat less effectively than by lifestyle modification. Lifestyle changes and metformin are reported to be cost-effective interventions, but whether delay or prevention of type 2 diabetes will result in lower rates of cardiovascular disease and diabetes microvascular complications will require longer-term follow-up studies.

Schwarz PE, Greaves CJ, Lindstrom J, et al. Nonpharmacologic interventions for the prevention of type 2 diabetes mellitus. *Nat Rev Endocrinol*. 2012;8:363-373.

5. A 28-year-old woman with type 1 diabetes since the age of 12 years is considering having a child. Currently, her blood glucose is reasonably well controlled, although she admits this was not the case during her teens and early 20s, when her HbA_{1c} was in the 9 to 11% range. She has mild background diabetic retinopathy, normal blood pressure, urine albumin-to-creatinine ratio of 25 mg/g, and normal findings on foot examination. Which of the following is true?

A. She should delay pregnancy until she has achieved optimal glucose control (HbA_{1c} approximately 6.5%).
B. She should be treated with an angiotensin-converting enzyme inhibitor to prevent progression of renal disease during pregnancy.
C. Progression of her retinopathy during pregnancy is likely to result in vision loss.
D. The risk of her child's developing type 1 diabetes is 25 to 50%.
E. She should be advised to avoid pregnancy because of the risk of both maternal and fetal complications.

Answer: A Although pregnancies in women with type 1 diabetes are generally considered "high risk," the outlook for patients with minimal complications and good metabolic control is good. Women with advanced renal disease (proteinuria, reduced glomerular filtration rate) or proliferative retinopathy may experience rapid progression during pregnancy because of the influence of hormonal and hemodynamic changes and should be monitored closely by specialists. Use of angiotensin-converting enzyme inhibitors is contraindicated during pregnancy because of the risk of fetal renal damage. The key to successful pregnancy outcomes is achieving optimal glucose control before conception because the developing fetus is most susceptible to the teratogenic effects of hyperglycemia in the first 6 to 8 weeks of pregnancy, before the time that most women are aware of being pregnant. Maintaining strict glucose control during the pregnancy will reduce the risk of fetal complications, such as macrosomia and hyperbilirubinemia. Many patients benefit from use of an insulin pump and continuous glucose monitoring during this time. Although a child of a mother with type 1 diabetes is at increased risk of diabetes compared with the general population, the risk is less than 10%.