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## PRINCIPLES OF INTERNAL MEDICINE

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## VOLUME I


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Weight-loss surgeries have traditionally been classified into three categories on the basis of anatomic changes: restrictive, restrictive malabsorptive, and malabsorptive. More recently, however, the clinical benefits of bariatric surgery in achieving weight loss and alleviating metabolic comorbidities have been attributed largely to changes in the physiologic responses of gut hormones, bile acid metabolism, the microbiota, and adipose tissue metabolism. Metabolic effects resulting from bypassing the foregut include altered responses of ghrelin, GLP-1, peptide YY3-36, and oxyntomodulin. Additional effects on food intake and body weight control may be attributed to changes in vagal signaling. The loss of fat mass, particularly visceral fat, is associated with multiple metabolic, adipokine, and inflammatory changes that include improved insulin sensitivity and glucose disposal; reduced free fatty acid flux; increased adiponectin levels; and decreased interleukin 6, tumor necrosis factor α, and high-sensitivity C-reactive protein levels.

Restrictive surgeries limit the amount of food the stomach can hold and slow the rate of gastric emptying. *Laparoscopic adjustable gastric banding* is the prototype of this category. The first banding device, the LAP-BAND, was approved for use in the United States in 2001. In contrast to previous devices, this band has a diameter that is adjustable by way of its connection to a reservoir that is implanted under the skin. Injection of saline into the reservoir and removal of saline from the reservoir tighten and loosen the band's internal diameter, respectively, thus changing the size of the gastric opening. Although the mean percentage of total body weight lost at 5 years is estimated at 20–25%, longer-term follow-up has been more disappointing, leading to near abandonment of the procedure. In the *laparoscopic sleeve gastrectomy*, the stomach is restricted by stapling and dividing it vertically, removing ~80% of the greater curvature and leaving a slim banana-shaped remnant stomach along the lesser curvature. Weight loss after this procedure is superior to that after laparoscopic adjustable gastric banding.

The three restrictive-malabsorptive bypass procedures combine the elements of gastric restriction and selective malabsorption: Roux-en-Y gastric bypass, biliopancreatic diversion, and biliopancreatic diversion with duodenal switch (Fig. 402-3). Roux-en-Y is the most commonly undertaken and most accepted bypass procedure. These procedures are routinely performed by laparoscopy.

These procedures generally produce a 30–35% average total body weight loss at 12–18 months followed by variable weight regain thereafter. Significant improvement in multiple obesity-related comorbid conditions, including type 2 diabetes, hypertension, dyslipidemia, obstructive sleep apnea, quality of life, and long-term cardiovascular events, has been reported. A meta-analysis of controlled clinical trials comparing bariatric surgery versus no surgery showed that surgery was associated with a reduced odds ratio (OR) risk of global mortality (OR = 0.55), cardiovascular death (OR = 0.58), and all-cause mortality (OR = 0.70).

Among the observed improvements in comorbidities, the prevention and treatment of type 2 diabetes resulting from bariatric surgery have garnered the most attention. Fifteen-year data from the Swedish Obese Subjects study demonstrated a marked reduction (i.e., by 78%) in the incidence of type 2 diabetes development among obese patients who underwent bariatric surgery. Multiple randomized controlled studies have shown greater weight loss and more improved glycemic control from 1 and 5 years among surgical patients than among patients receiving conventional medical therapy. A retrospective cohort study of >4000 adults with diabetes found that, overall, 68.2% of patients experienced an initial complete remission of type 2 diabetes within 5 years after surgery. However, among these patients, one-third redeveloped type 2 diabetes within 5 years. Patients with earlier-stage type 2 diabetes (i.e., those who do not need insulin, with shorter-duration disease, and with lower hemoglobin $A_{1c}$) appear to have better improvement after bariatric surgery. The rapid improvement seen in diabetes after bariatric surgery is thought to be due to caloric restriction, reduced insulin resistance, and surgery-specific effects on glucose homeostasis brought about by alteration of gut hormones.

The mortality rate from bariatric surgery is generally <1% but varies with the procedure, the patient's age and comorbid conditions, and the experience of the surgical team. The most common surgical complications include stomal stenosis or marginal ulcers (occurring in 5–15% of patients) that present as prolonged nausea and vomiting after eating or inability to advance the diet to solid foods. These complications typically are treated by endoscopic balloon dilation and acid suppression therapy, respectively. For patients who undergo laparoscopic adjustable gastric banding, there are no intestinal absorptive abnormalities other than mechanical reduction in gastric size and outflow. Therefore, selective deficiencies are uncommon unless eating habits become unbalanced. In contrast, the restrictive-malabsorptive procedures carry an increased risk for micronutrient deficiencies of vitamin $B_{12}$, iron, folate, calcium, and vitamin D. Patients with restrictive-malabsorptive procedures require lifelong supplementation with these micronutrients.

***Intraluminal Gastric Balloons*** Three gastric balloon devices are approved for weight loss that are either placed in the stomach endoscopically (the REHAPE and ORBERA devices) or swallowed (OBALON). Efficacy of the devices at 6 months, based on a pooled weighted-mean percent weight loss, was 9.7%, and the control-subtracted percent weight loss was 5.6%. The devices are approved only for up to 6 months of use in adults with a BMI of 30–40 kg/m$^2$. Adverse effects include nausea, vomiting, and abdominal pain.

## FURTHER READING


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# 403 Diabetes Mellitus: Diagnosis, Classification, and Pathophysiology

**Alvin C. Powers, Kevin D. Niswender, Carmella Evans-Molina**

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. In the United States, DM is the leading cause of end-stage renal disease

(ESRD), nontraumatic lower-extremity amputations, and adult blindness. Persons with diabetes are at increased risk for cardiovascular disease, which is the main cause of morbidity and mortality in this population.

## CLASSIFICATION

DM is classified on the basis of the pathogenic process leading to hyperglycemia **(Table 403-1)**. There are two broad categories of DM, designated as either type 1 or type 2 DM. However, there is increasing recognition of other forms of diabetes in which the molecular pathogenesis is better understood and may be associated with a single gene defect. These alternative forms as well as other "atypical" forms may share features of type 1 and/or type 2 DM. Type 1 DM develops as a result of autoimmunity against the insulin-producing beta cells, resulting in insulin deficiency. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased hepatic glucose production. Defects in insulin action and/or secretion give rise to the common phenotype of hyperglycemia in type 2 DM and have important therapeutic implications now that pharmacologic agents are available to target specific metabolic derangements. Both type 1 and type 2 diabetes are preceded by a period of progressive worsening of glucose homeostasis, followed by the development of hyperglycemia that exceeds the threshold for clinical diagnosis. In terms of type 2 diabetes, this phase is referred to as prediabetes and is more specifically classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) **(Fig. 403-1)**. Recently, three distinct stages of type 1 DM have been defined based on the development of autoantibodies against pancreatic beta cell antigens or the development of worsening dysglycemia (discussed below).

**TABLE 403-1 Etiologic Classification of Diabetes Mellitus**

I. Type 1 diabetes (immune-mediated beta cell destruction, usually leading to absolute insulin deficiency)

II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

III. Specific types of diabetes (monogenic or MODY)

- A. Genetic defects of beta cell development or function characterized by mutations in:
  1. Hepatocyte nuclear transcription factor (HNF) 4α
  2. Glucokinase
  3. HNF-1α
  4. Insulin promoter factor-1, HNF-1β, NeuroD1, and other pancreatic islet regulators/proteins such as *KLF11, PAX4, BLK, GATA4, GATA6, SLC2A2* (GLUT2), *RFX6, GLIS3*
  5. Insulin, leading to permanent neonatal diabetes
  6. Subunits of ATP-sensitive potassium channel, leading to permanent neonatal diabetes
  7. Mitochondrial DNA
- B. Transient neonatal diabetes
- C. Diseases of the exocrine pancreas—pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, mutations in carboxyl ester lipase
- D. Genetic defects in insulin action, including type A insulin resistance, Leprechaunism, Rabson-Mendenhall syndrome, lipodystrophy syndromes
- E. Endocrinopathies—acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma
- F. Drug- or chemical-induced—glucocorticoids, calcineurin and mTOR inhibitors (after organ transplantation), vacor (a rodenticide), pentamidine, nicotinic acid, diazoxide, β-adrenergic agonists, thiazides, hydantoins, asparaginase, α-interferon, protease inhibitors, antipsychotics (atypicals and others), epinephrine
- G. Infections—congenital rubella, cytomegalovirus, coxsackievirus
- H. Uncommon forms of immune-mediated diabetes—"stiff-person" syndrome, anti-insulin receptor antibodies
- I. Other genetic syndromes sometimes associated with diabetes—Wolfram syndrome, Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome

IV. Gestational diabetes mellitus (GDM)

*Abbreviation:* MODY, maturity-onset diabetes of the young or monogenic diabetes; see text.

*Source:* Data from American Diabetes Association. Standards of medical care in diabetes–2014. Diabetes Care 37:S14, 2014.

| | Normal glucose tolerance | Hyperglycemia | | |
|---|---|---|---|---|
| | | Pre-diabetes* | Diabetes Mellitus | |
| | | Impaired fasting glucose or impaired glucose tolerance | Not insulin requiring | Insulin required for control / Insulin required for survival |
| | | | Symptoms of diabetes + random blood glucose concentration ≥11.1 mmol/L (200 mg/dL)[a] | |
| FPG | <5.6 mmol/L (100 mg/dL) | 5.6–6.9 mmol/L (100–125 mg/dL) | ≥7.0 mmol/L (126 mg/dL)[b] | |
| HbA1C | <5.6% | 5.7–6.4% | ≥6.5%[c] | |
| 2-h PG | <7.8 mmol/L (140 mg/dL) | 7.8–11.0 mmol/L (140–199 mg/dL) | ≥11.1 mmol/L (200 mg/dL)[d] | |

**FIGURE 403-1 Spectrum of glucose homeostasis and diagnosis of diabetes mellitus (DM).** Glucose homeostasis is a spectrum from normal glucose tolerance (*left portion of figure*) to diabetes (*right portion of figure*) including type 1 DM, type 2 DM, specific types of diabetes, and gestational DM. The diagnostic criteria for diabetes are shown in the lower right portion of the figure and include the hemoglobin $A_{1c}$ ($HbA_{1c}$), the fasting plasma glucose (FPG), and the 2-h plasma glucose (PG) after a glucose challenge. In most types of DM, the individual traverses from normal glucose tolerance to impaired glucose tolerance to overt diabetes (these should be viewed not as abrupt categories but as a spectrum). Changes in glucose tolerance may be bidirectional in some types of diabetes. For example, individuals with type 2 DM may return to the impaired glucose tolerance category with weight loss; in gestational DM, diabetes may revert to impaired glucose tolerance or normal glucose tolerance after delivery. [a]Random is defined as without regard to time since the last meal. [b]Fasting is defined as no caloric intake for at least 8 h. [c]Hemoglobin A1c test should be performed in a laboratory using a method approved by the National Glycohemoglobin Standardization Program and correlated to the reference assay of the Diabetes Control and Complications Trial. Point-of-care hemoglobin A1c should not be used for diagnostic purposes. [d]The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water, not recommended for routine clinical use. Assessment of 1-h glucose may be helpful in diabetes risk prediction in individuals with cystic fibrosis or other forms of pancreatic disease. In the absence of unequivocal hyperglycemia and acute metabolic decompensation, the blood glucose criteria should be confirmed by repeat testing on a different day. These values do not apply to the diagnosis of gestational DM. *Some use the term *increased risk for diabetes* or *intermediate hyperglycemia* (World Health Organization) rather than *prediabetes. (Data from American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care 44:S15, 2021.)*

## OTHER TYPES OF DM

Other etiologies of DM include specific genetic defects in insulin secretion or action, metabolic abnormalities that impair insulin secretion, mitochondrial abnormalities, and a host of conditions that impair glucose tolerance (Table 403-1). *Maturity-onset diabetes of the young* (MODY) and *monogenic diabetes* are subtypes of DM characterized by autosomal dominant inheritance, early onset of hyperglycemia (usually <25 years; sometimes in neonatal period), and impaired insulin secretion (discussed below). Mutations in the insulin receptor cause a group of rare disorders characterized by severe insulin resistance.

DM may also develop as a result of cystic fibrosis or chronic pancreatitis, in which the islets become damaged from a primary pathologic process originating in the pancreatic exocrine tissue. Hormones that antagonize insulin action can lead to DM. Hyperglycemia is often a feature of endocrinopathies such as acromegaly and Cushing's disease. Viral infections have been implicated in pancreatic islet destruction but are an extremely rare cause of DM. A form of acute onset of type 1 diabetes, termed *fulminant diabetes*, has been noted in Japan and may be related to viral infection of the islets.

### GESTATIONAL DM

Glucose intolerance developing during the second or third trimester of pregnancy is classified as gestational diabetes mellitus (GDM). Insulin resistance is related to the metabolic changes of pregnancy, during which the increased insulin demands may lead to IGT or diabetes. The American Diabetes Association (ADA) recommends that diabetes diagnosed within the first trimester be classified as preexisting pregestational diabetes rather than GDM. In 2019, the International Diabetes Federation (IDF) estimated that 16% of pregnancies worldwide were affected by either GDM or preexisting DM. Most women with GDM revert to normal glucose tolerance postpartum but have a substantial risk (35–60%) of developing DM in the next 10–20 years. In addition, children born to a mother with GDM also have an increased risk of developing metabolic syndrome and type 2 DM later in life. Currently, the ADA recommends that women with a history of GDM undergo lifelong screening for the development of diabetes or prediabetes at least every 3 years.

### ATYPICAL DIABETES

It is increasingly recognized that some forms of diabetes have features of both type 1 and type 2 diabetes. These are distinct from monogenic forms (MODY) as they have not been linked to single gene defects. The development of a type 2 diabetes phenotype before puberty and a type 2 diabetes phenotype in very lean individuals are examples of atypical diabetes. An additional example is ketosis-prone diabetes, where individuals present with ketoacidosis, but do not require long-term exogenous insulin therapy. Many of these individuals are African American or Asian in heritage. Mechanisms underlying atypical forms of diabetes are being actively studied.

## EPIDEMIOLOGY AND GLOBAL CONSIDERATIONS

The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 463 million in 2019 **(Fig. 403-2)**. Based on current trends, the IDF projects that 642 million individuals will have diabetes by the year 2040 (see *http://www.idf.org/*). Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 DM is rising much more rapidly, presumably because of dietary changes and increasing obesity, reduced activity levels as countries become more industrialized, and aging of the population. The incidence of type 1 diabetes has been increasing at a rate of 3% per year worldwide, with clear geographic differences. The cause for this increase is not well understood, but type 1 DM is increasingly being diagnosed at younger ages. In 2019, the prevalence of diabetes in individuals aged 20–79 years worldwide was 9.3%, ranging from 4.7–12.2%. The countries with the greatest number of individuals with diabetes in 2019 were China (116.4 million), India (77 million), the United States (31 million), Pakistan (19.4 million), Brazil (16.8 million), and Mexico (12.8 million). In the most recent estimate for the United States (2020), the Centers for Disease Control and Prevention (CDC) estimated that 10.5% of the population had diabetes. Diabetes affected 13% of all U.S. adults, and as many as 34% or 88 million U.S. adults had prediabetes. Approximately 21.4% of U.S. adults with diabetes in the United States were undiagnosed; globally, it is estimated that as many as 50% of individuals with diabetes may be undiagnosed. The prevalence of DM increases with age. The prevalence of DM in the United States was estimated to be 0.25% in individuals age <20 years, 4.2% in persons aged 18–44 years, and 17.5% in persons 45–64 years old. In individuals aged >65 years, the prevalence of DM was 26.8%. Similar age-related trends have been observed worldwide.

There is considerable geographic variation in the incidence of both type 1 and type 2 DM. Currently, Scandinavia, followed by Sardina and Portugal, have the highest incidence of type 1 DM; the lowest incidence is in the Pacific Rim where it is twenty- to thirtyfold lower. Northern Europe and the United States have an intermediate rate. Much of the increased risk of type 1 DM is believed to reflect the frequency of high-risk human leukocyte antigen (HLA) alleles among ethnic groups in different geographic locations. However, now populations less enriched with these classic high-risk HLA alleles are experiencing more rapid increases in type 1 DM incidence, suggesting an influence of environmental factors.

The prevalence of type 2 DM and its harbinger, IGT, is highest in certain Pacific islands and the Middle East and intermediate in countries such as India and the United States. This variability is likely due to genetic, behavioral, and environmental factors. DM prevalence also varies among different ethnic populations within a given country, with indigenous populations usually having a greater incidence of diabetes than the general population of the country. For example, the CDC estimated that the age-adjusted prevalence of DM in the United States (age >20 years; 2017–2018) was 7.5% in non-Hispanic whites, 9.2% in Asian Americans, 12.5% in Hispanics, and 11.7% in non-Hispanic blacks, but it exceeds 14% in American-Indian and Alaskan native populations. The onset of type 2 DM occurs, on average, at an earlier age in ethnic groups other than non-Hispanic whites. In Asia, the prevalence of diabetes is increasing rapidly, with an onset at a lower body mass index (BMI) and younger age, greater visceral adiposity, and reduced insulin secretory capacity.

Diabetes is a major cause of mortality. In recent years, diabetes has been listed as the seventh leading cause of death in the United States, but several studies indicate that diabetes-related deaths are likely underreported. In 2019, data from the IDF suggest that diabetes was responsible for nearly 4.2 million deaths worldwide, accounting for 11.3% of global all-cause mortality in adults aged 20–79 years. Diabetes also has important economic implications. In 2019, it was estimated that $760 billion of health care expenditures worldwide were spent on diabetes (a range of 8–19% of total expenditures across regions). Up to 75% of individuals with diabetes live in low- or middle-income countries.

## DIAGNOSIS

Glucose tolerance is classified into three broad categories: normal glucose homeostasis, impaired glucose homeostasis, or DM (Fig. 403-1). Glucose tolerance can be assessed using the fasting plasma glucose (FPG), the response to oral glucose challenge, or the hemoglobin $A_{1c}$ ($HbA_{1c}$). An FPG <5.6 mmol/L (100 mg/dL), a plasma glucose <7.9 mmol/L (140 mg/dL) following an oral glucose challenge, and an $HbA_{1c}$ <5.7% are considered to define normal glucose tolerance. The International Expert Committee with members appointed by

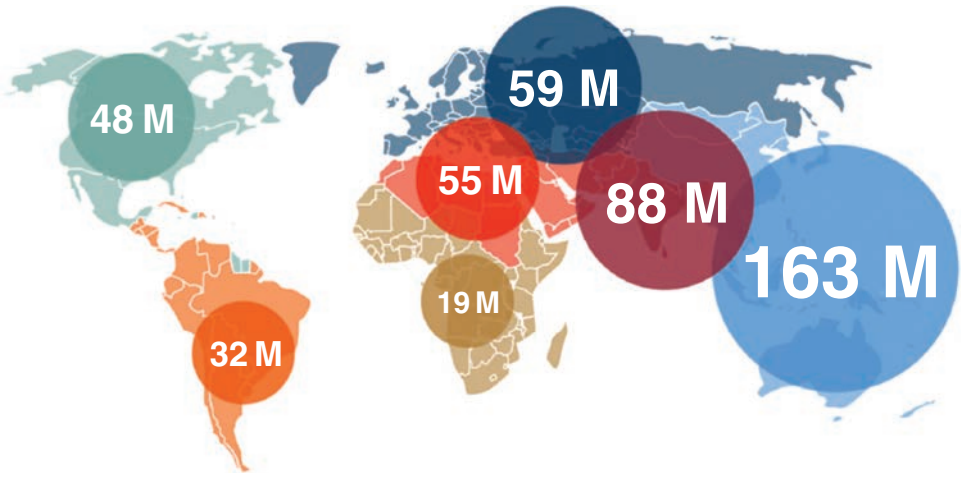


**FIGURE 403-2 Worldwide prevalence of diabetes mellitus.** Global estimate is 463 million individuals with diabetes in 2019. Regional estimates of the number of individuals with diabetes (20–79 years of age) are shown (2019). *(Data from the IDF Diabetes Atlas, 9th ed. The International Diabetes Federation; 2019.)*

**TABLE 403-2 Criteria for Screening for Type 2 Diabetes Mellitus in Adults**

1. Consider testing in overweight or obese (BMI ≥25 kg/m$^2$, ≥23 kg/m$^2$ in Asian Americans, or other ethnically relevant definition who have these risk factors:
   - Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
   - Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - Hypertension (blood pressure ≥140/90 mmHg)
   - HDL cholesterol level <35 mg/dL (0.90 mmol/L) and/or a triglyceride level >250 mg/dL (2.82 mmol/L)
   - Polycystic ovary syndrome or acanthosis nigricans
   - History of cardiovascular disease
   - Physical inactivity
   - Other condition associated with insulin resistance (severe obesity, acanthosis nigricans)
2. Individuals with previously identified IFG, IGT, or a hemoglobin $A_{1c}$ of 5.7–6.4% should be screened annually.
3. Women who had GDM should be screened at least every 3 years.
4. For other individuals, initiate testing at 45 years of age and repeat every 3 years.
5. Individuals with HIV

*Abbreviations:* BMI, body mass index; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; HIV, human immunodeficiency virus.

*Source:* Adapted with permission from American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of medical care in diabetes-2021. Diabetes Care 44:S15, 2021.

the ADA, the European Association for the Study of Diabetes, and the IDF have issued diagnostic criteria for DM **(Table 403-2)** based on the following premises: (1) the FPG, the response to an oral glucose challenge (oral glucose tolerance test [OGTT]), and $HbA_{1c}$ differ among individuals, and (2) DM is defined as the level of glycemia at which diabetes-specific complications occur rather than deviation from a population-based mean. For example, the prevalence of retinopathy in Native Americans (Pima Indian population) begins to increase at an FPG >6.4 mmol/L (116 mg/dL) **(Fig. 403-3)**.

Abnormal glucose homeostasis can be diagnosed by three distinct criteria (Fig. 403-1). First, *impaired fasting glucose* (IFG) is defined as a fasting plasma glucose (FPG) value of 5.6–6.9 mmol/L (100–125 mg/dL). Second, *impaired glucose tolerance* (IGT) is defined as a plasma glucose level of 7.8–11 mmol/L (140–199 mg/dL) following an oral glucose challenge. Third, an $HbA_{1c}$ of 5.7–6.4% reflects dysglycemia by all mechanisms. While an $HbA_{1c}$ of 5.7–6.4%, IFG, and IGT do not identify the same individuals (i.e., different biologic mechanisms involved), individuals in all three groups are at greater risk of progressing to type 2 DM, have an increased risk of cardiovascular disease, and should be counseled about ways to decrease these risks (see below). Some use the terms *prediabetes*, *increased risk of diabetes*, or *intermediate hyperglycemia* (World Health Organization) and slightly different metrics for this category.

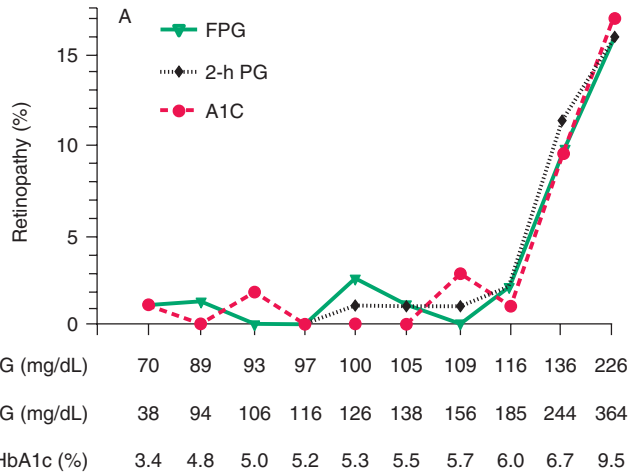


**FIGURE 403-3 Relationship of diabetes-specific complication and glucose tolerance.** This figure shows the incidence of retinopathy in Pima Indians as a function of the fasting plasma glucose (FPG), the 2-h plasma glucose after a 75-g oral glucose challenge (2-h PG), or the hemoglobin $A_{1c}$ ($HbA_{1c}$). Note that the incidence of retinopathy greatly increases at a FPG >116 mg/dL, a 2-h PG of 185 mg/dL, or an $HbA_{1c}$ >6.5%. (Blood glucose values are shown in mg/dL; to convert to mmol/L, divide value by 18.) *(Modified with permission from Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 26:S5, 2003.)*

It is important to recognize that these values for the FPG, the glucose following an oral glucose challenge, and $HbA_{1c}$ are continuous rather than discrete variables; risk for comorbidities increases continuously rather than discretely by diagnostic category. A FPG ≥7.0 mmol/L (126 mg/dL), a glucose ≥11.1 mmol/L (200 mg/dL) 2 h after an oral glucose challenge, or an $HbA_{1c}$ ≥6.5% meets the criteria for the diagnosis of DM (Fig. 403-1). A random plasma glucose concentration ≥11.1 mmol/L (200 mg/dL) accompanied by classic symptoms of DM (polyuria, polydipsia, weight loss) is also sufficient for the diagnosis of DM. The current criteria for the diagnosis of DM emphasize the $HbA_{1c}$ and the FPG as the most reliable and convenient tests for identifying DM in asymptomatic individuals. However, some individuals may meet criteria for one test but not the other. Also, it is important to note that race and ethnicity may impact the reliability of $HbA_{1c}$ levels. For example, African Americans have a higher $HbA_{1c}$ value compared to non-Hispanic whites with a similar level of glycemia. An OGTT, although a valid means for diagnosing DM, is not often used in routine clinical care with the exception of pregnancy care and screening for gestational diabetes.

The diagnosis of DM has profound implications for an individual from both a medical and a financial standpoint. Thus, abnormalities on screening tests for diabetes should be repeated before making a definitive diagnosis of DM, unless acute metabolic derangements or a markedly elevated plasma glucose are present. These criteria also allow for the diagnosis of DM to be withdrawn in situations when the glucose intolerance reverts to normal.

### SCREENING

Widespread use of the FPG or the $HbA_{1c}$ as a screening test for type 2 DM is recommended because (1) a large number of individuals who meet the current criteria for DM are asymptomatic and unaware that they have the disorder, (2) epidemiologic studies suggest that type 2 DM may be present for up to a decade before diagnosis, (3) some individuals with type 2 DM have one or more diabetes-specific complications at the time of their diagnosis, (4) treatment of type 2 DM may favorably alter the natural history of DM, and (5) diagnosis of prediabetes should spur efforts for diabetes prevention. The ADA recommends screening all individuals aged >45 years every 3 years and screening individuals at an earlier age if they are overweight (BMI >25 kg/m$^2$ or ethnically relevant definition for overweight) and have one additional risk factor for diabetes. Although a number of immunologic markers for type 1 DM are becoming available (discussed below), their routine use outside a clinical trial is discouraged, pending the identification of clinically beneficial interventions for individuals at high risk for developing type 1 DM.

## REGULATION OF GLUCOSE HOMEOSTASIS

### OVERALL REGULATION OF GLUCOSE HOMEOSTASIS

Glucose homeostasis reflects a balance between energy intake from ingested food, hepatic glucose production (gluconeogenesis), and peripheral tissue glucose uptake and utilization. Insulin is the most important regulator of this metabolic equilibrium, but neural input, metabolic signals, and other hormones (e.g., glucagon) result in integrated control of glucose supply and utilization **(Fig. 403-4)**. The organs that regulate glucose and lipids communicate by neural and humoral mechanisms with fat and muscle producing adipokines, myokines, and metabolites that influence liver function. In the fasting

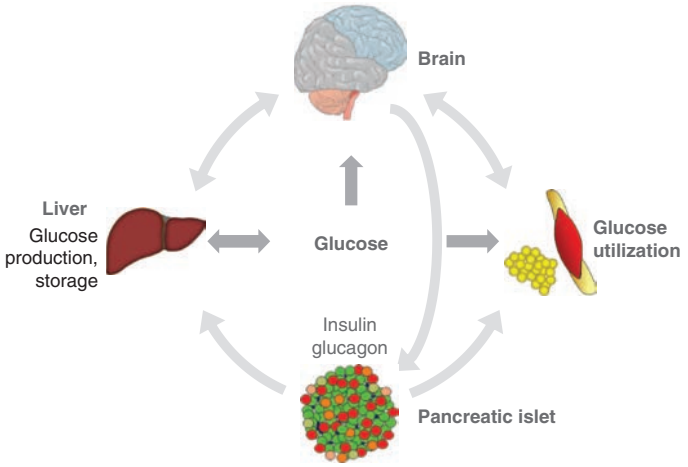


**FIGURE 403-4 Regulation of glucose homeostasis.** The organs shown contribute to glucose utilization, production, or storage. See text for a description of the communications (*arrows*), which can be neural or humoral. Although not shown, the GI tract and bone produce factors that influence glucose homeostasis.

state, low insulin levels, together with modest increases in glucagon, increase glucose production by promoting hepatic gluconeogenesis and glycogen breakdown (glycogenolysis). In parallel, glucose uptake in insulin-sensitive tissues (skeletal muscle and fat) is reduced, and there is increased mobilization of gluconeogenic precursors such as amino acids and free fatty acids (lipolysis). Under normal conditions alpha cells increase glucagon secretion only when blood glucose or insulin levels are low or during exercise, but it is increased in fasting and postprandially in DM and stimulates excess glycogenolysis and gluconeogenesis by the liver and to a small degree by the renal medulla **(Chap. 406)**. Conversely, in healthy people, the postprandial glucose load elicits a rise in insulin and fall in glucagon, leading to optimized glucose disposal. Insulin, an anabolic hormone, promotes the storage of carbohydrate and fat and protein synthesis. The major portion of postprandial glucose is utilized by skeletal muscle, an effect of insulin-stimulated glucose uptake. Other tissues, most notably the brain, utilize glucose in an insulin-independent fashion. Factors secreted by skeletal myocytes, adipocytes (e.g., leptin, resistin, adiponectin), and bone also influence glucose homeostasis.

## INSULIN BIOSYNTHESIS

Insulin, produced by the beta cells of the pancreatic islets, is initially synthesized as a single-chain 86-amino-acid precursor polypeptide, preproinsulin. Subsequent proteolytic processing removes the amino-terminal signal peptide, giving rise to proinsulin. Proinsulin is structurally related to insulin-like growth factors I and II, which bind weakly to the insulin receptor. Cleavage of an internal 31-residue fragment from proinsulin generates C-peptide with the A (21 amino acids) and B (30 amino acids) chains of insulin being connected by disulfide bonds. The mature insulin molecule and C-peptide are stored together and co-secreted from secretory granules in the beta cells. Because C-peptide is cleared more slowly than insulin, it is a useful marker of insulin secretion and allows discrimination of endogenous and exogenous sources of insulin in the evaluation of hypoglycemia **(Chaps. 406 and 84)**. Elevated levels of serum proinsulin have been observed in both type 1 and 2 DM and are thought to be indicative of beta cell dysfunction. Pancreatic beta cells co-secrete islet amyloid polypeptide (IAPP) or amylin, a 37-amino-acid peptide, along with insulin. The role of IAPP in normal physiology is incompletely defined, but it is the major component of the amyloid fibrils found in the islets of patients with type 2 diabetes, and an analogue is sometimes used in treating type 1 and type 2 DM **(Chap. 404)**.

## INSULIN SECRETION

Glucose is the key regulator of insulin secretion by the pancreatic beta cell, although amino acids, ketones, various nutrients, gastrointestinal peptides, and neurotransmitters also influence insulin secretion. Glucose levels >3.9 mmol/L (70 mg/dL) stimulate insulin synthesis,

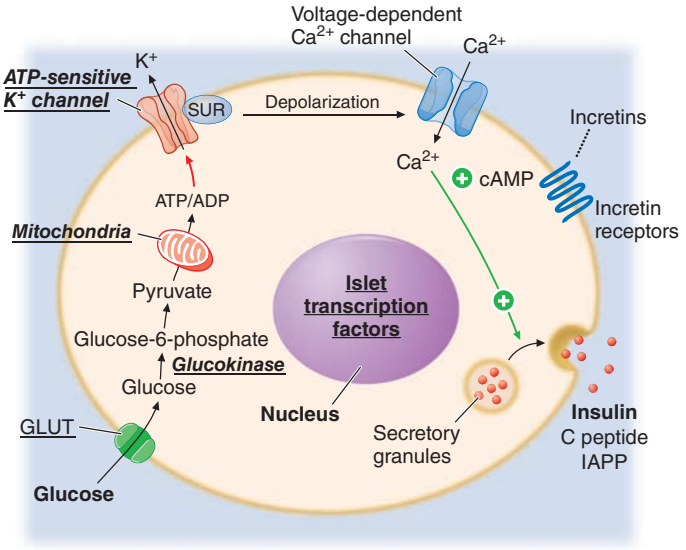


**FIGURE 403-5 Mechanisms of glucose-stimulated insulin secretion and abnormalities in diabetes.** Glucose and other nutrients regulate insulin secretion by the pancreatic beta cell. Glucose is transported by a glucose transporter (GLUT1 and/or GLUT2 in humans, GLUT2 in rodents); subsequent glucose metabolism by the beta cell alters ion channel activity, leading to insulin secretion. The SUR receptor is the binding site for some drugs that act as insulin secretagogues. Mutations in the events or proteins underlined are a cause of monogenic forms of diabetes. ADP, adenosine diphosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; IAPP, islet amyloid polypeptide or amylin; SUR, sulfonylurea receptor.

primarily by enhancing protein translation and processing. Glucose stimulation of insulin secretion begins with its transport into the beta cell by a facilitative glucose transporter **(Fig. 403-5)**. Glucose phosphorylation by glucokinase is the rate-limiting step that controls glucose-regulated insulin secretion. Further metabolism of glucose-6-phosphate via glycolysis generates ATP, which inhibits the activity of an ATP-sensitive $K^+$ channel. This channel consists of two separate proteins: one is the binding site for certain oral hypoglycemics (e.g., sulfonylureas, meglitinides); the other is an inwardly rectifying $K^+$ channel protein (Kir6.2). Inhibition of this $K^+$ channel induces beta cell membrane depolarization, which opens voltage-dependent calcium channels (leading to an influx of calcium) and stimulates insulin secretion. Insulin secretion occurs in two phases, a rapid first-phase response, and a more prolonged second phase. Impaired first-phase insulin responses are among the earliest detectable abnormalities during the progression of both T1DM and T2DM. A number of metabolic pathways internal to the beta cell as well as external cues amplify glucose-stimulated insulin secretion. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are incretin hormones that bind specific receptors on the beta cell to stimulate insulin secretion through cyclic AMP production, but they have this effect only when the blood glucose is above the fasting level. Incretin hormones also suppress glucagon production and secretion. Incretin analogues or pharmacologic agents that prolong the activity of endogenous GLP-1 are used to treat type 2 DM. Classically, GLP-1 release was thought to occur solely from neuroendocrine L-cells of the gastrointestinal tract following food ingestion. However, recent preclinical studies suggest that intraislet production of GLP-1 from alpha cells may play a role in the regulation of insulin secretion.

## INSULIN ACTION

Insulin is secreted into the portal venous system and acts to suppress endogenous hepatic glucose production and increase hepatic glucose uptake. A large portion (50%) of secreted insulin is cleared by the liver in this first pass, yielding a portal to peripheral insulin concentration gradient of ~2:1, with important implications for the clinical use of exogenous insulin **(Ch. 404)**. Uncleared insulin enters the systemic circulation where it binds to receptors in peripheral target tissues such as skeletal muscle and adipose. Insulin binding to its receptor stimulates

intrinsic tyrosine kinase activity, leading to receptor autophosphorylation and the recruitment of intracellular signaling molecules, including the important insulin receptor substrates (IRS). IRS and other adaptor proteins initiate a complex cascade of phosphorylation and dephosphorylation reactions, resulting in the widespread metabolic and mitogenic effects of insulin. As an example, activation of the phosphatidylinositol-3′-kinase (PI-3-kinase) pathway stimulates translocation of a facilitative glucose transporter (e.g., GLUT4) to the cell surface, an event that is crucial for glucose uptake by skeletal muscle and fat. Activation of other insulin receptor signaling pathways induces glycogen synthesis, protein synthesis, lipogenesis, and regulation of various genes in insulin-responsive cells.

## PATHOGENESIS

### TYPE 1 DM

Type 1 DM is the result of interactions of genetic, environmental, and immunologic factors that ultimately lead to immune-mediated destruction of the pancreatic beta cells and insulin deficiency. Type 1 DM can develop at any age. Most, but not all, individuals with type 1 DM have evidence of islet-directed autoimmunity, which is detected by the presence of autoantibodies against beta cell antigens in the blood. The presence of two or more autoantibodies is now designated as stage 1 T1DM **(Fig. 403-6)**. The temporal decline of beta cell function and mass preceding the development of type 1 DM is shown schematically in Fig. 403-6. In susceptible individuals, the autoimmune process is thought to be triggered by an infectious or environmental stimulus. In the majority of patients, autoantibodies against beta cell antigens appear after this triggering event, followed by progressive loss of insulin secretion. The rate of decline in beta cell function varies widely among individuals, with some patients progressing rapidly to clinical diabetes and others evolving to diabetes more slowly and over a period of several years. Features of diabetes do not become evident until a threshold loss of insulin secretion and beta cell mass occurs. Autopsy studies suggest the degree of loss of beta cell mass is variable at the time of disease presentation. At this point, residual, functional beta cells exist but are insufficient in number and quality to maintain glucose tolerance. The events that trigger the transition from glucose intolerance to frank diabetes are often associated with increased insulin requirements, as might occur during infections or at puberty. After the initial clinical presentation of type 1 DM, a "honeymoon" phase may ensue during which time glycemic control is achieved with modest doses of insulin or, rarely, insulin is not needed. However, this fleeting phase of endogenous insulin production from residual beta cells disappears and the individual becomes insulin deficient. Many individuals with long-standing type 1 DM produce a small amount of insulin (as reflected by C-peptide production), and autopsy studies show that beta cells can persist in the pancreas decades after diagnosis.

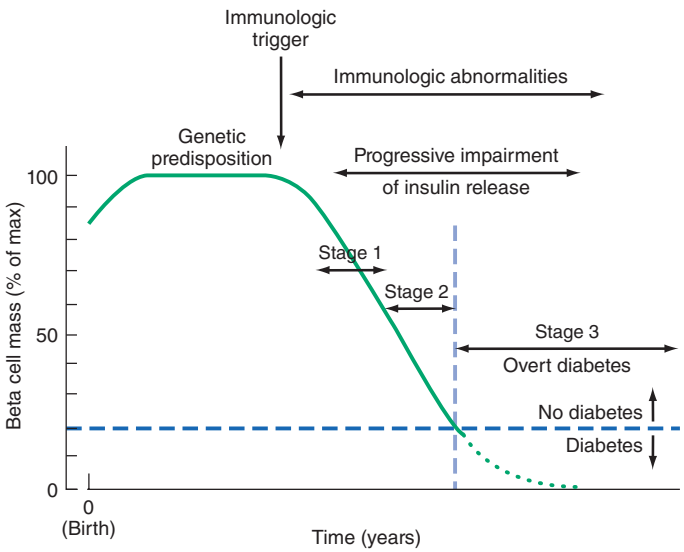


**FIGURE 403-6 Temporal model for development of type 1 diabetes.** Individuals with a genetic predisposition are exposed to a trigger that initiates an autoimmune process, resulting in the development of islet autoantibodies and a gradual decline in beta cell function and mass. Stage 1 disease is characterized by the development of two or more islet cell autoantibodies but the maintenance of normoglycemia. Stage 2 disease is defined by continued autoimmunity and the development of dysglycemia. Stage 3 is defined by the development of hyperglycemia that exceeds the diagnostic criteria for the diagnosis of diabetes. The downward slope of the beta cell function varies among individuals and may not be continuous. A "honeymoon" phase may be seen in the first 1 or 2 years after the onset of diabetes and is associated with reduced insulin requirements. *(Modified with permission from ER Kaufman: Medical Management of Type 1 Diabetes, 6th ed. Alexandria, VA: American Diabetes Association; 2012.)*

### GENETIC CONSIDERATIONS

Susceptibility to type 1 DM involves multiple genes. The concordance of type 1 DM in identical twins ranges from 30–70%, indicating that additional modifying factors are likely involved in determining whether diabetes develops. The major susceptibility gene for type 1 DM is located in the HLA region on chromosome 6. Polymorphisms in the HLA complex account for approximately 50% of the genetic risk of developing type 1 DM. This region contains genes that encode the class II major histocompatibility complex (MHC) molecules, which present antigen to helper T cells and thus are involved in initiating the immune response **(Chap. 349)**. The ability of class II MHC molecules to present antigen is dependent on the amino acid composition of their antigen-binding sites. Amino acid substitutions may influence the specificity of the immune response by altering the binding affinity of different antigens for class II molecules.

Many individuals with type 1 DM have the HLA DR3 and/or DR4 haplotype. Refinements in genotyping of HLA loci have shown that the haplotypes DQA1*0301, DQB1*0302, and DQB1*0201 are most strongly associated with type 1 DM. These haplotypes are present in 40% of children with type 1 DM as compared to 2% of the U.S. population without type 1 DM. However, most individuals with predisposing haplotypes do not develop diabetes.

In addition to MHC class II associations, genome-wide association studies have identified more than 60 additional genetic loci that contribute susceptibility to type 1 DM (i.e., polymorphisms in the promoter region of the insulin gene, the CTLA-4 gene, interleukin 2 receptor, and PTPN22, etc.). Combined assessment of HLA and non-HLA loci using genetic risk scores has been used to improve prediction of type 1 diabetes risk. Notably, among recent cohorts of individuals with new-onset type 1 diabetes, there is a decreased representation of the highest-risk HLA alleles and increasing penetrance of disease in genotypes classically associated with lower risk, suggesting environmental factors may have an increasing role in disease pathogenesis. Genes that confer protection against the development of the disease also exist. The haplotype DQA1*0102, DQB1*0602 is extremely rare in individuals with type 1 DM (<1%) and appears to provide protection from type 1 DM.

Although the risk of developing type 1 DM is increased in relatives of individuals with the disease, the risk is relatively low: 1–9% if the parent has type 1 DM and 6–7% in a sibling (depending on which HLA haplotypes are shared). Hence, the majority of individuals with type 1 DM (>90%) do not have a relative with this disorder.

**Pathophysiology** Pathologically, the pancreatic islets demonstrate a modest infiltration of lymphocytes (a process termed *insulitis*); however, the frequency of insulitis is heterogeneous both within and between individuals. Studies of the autoimmune process have identified the following abnormalities in the innate and adaptive arms of the immune system: (1) islet cell autoantibodies (ICAs); (2) activated lymphocytes in the islets, and peripancreatic lymph nodes; (3) T lymphocytes that proliferate when stimulated with islet proteins; and (4) release of cytokines within the insulitis. Islet cell autoantibodies (ICAs) are a composite of several different antibodies directed at pancreatic islet molecules such as GAD, insulin, IA-2/ICA-512, and ZnT-8, and serve as a marker of the autoimmune process of type 1 DM. Testing for ICAs can be useful in classifying the type of DM as type 1 as they are

present in the majority of individuals (>85%) diagnosed with new-onset type 1 DM. ICAs can also identify nondiabetic individuals at risk for developing type 1 DM, although their use for this purpose has been restricted mostly to research studies. In children with high genetic risk followed as part of several birth cohort studies, the presence of two or more ICAs was associated with a nearly 70% risk of developing type 1 DM after 10 years of follow-up and an 80% risk of developing diabetes after 15 years of follow-up. These observations led to a revision in the staging system for type 1 DM (Fig. 403-5), in which the development of multiple autoantibodies is now defined as the onset of stage 1 type 1 DM. While ICAs can be detected in the serum, and their presence is an important biomarker of type 1 diabetes risk, the antibodies do not have a direct role in beta cell death. Beta cell destruction is mediated by direct CD8+ T cell–mediated cytotoxicity. Beta cells may exacerbate this process through the development of modified proteins or "neoantigens" and through increased presentation of these antigens on their cell surface via upregulation of MHC class I molecules. In addition, beta cells may be damaged by the toxic effects of cytokines (i.e., tumor necrosis factor α [TNF-α], interferon γ, and interleukin 1 [IL-1]) as well as reactive oxygen species generated by infiltrating immune cells. Efforts to suppress the autoimmune process at the time of diagnosis of diabetes have largely been ineffective or only temporarily effective in slowing beta cell destruction. Thus, increased emphasis has now been placed on intervening earlier in the disease course (i.e., during stage 1 and 2 disease; Fig. 403-6). In support of this notion, a single 14-day course of teplizumab, an Fc receptor-nonbinding anti-CD3 monoclonal antibody, delayed the onset of stage 3 T1D in high-risk individuals with multiple autoantibodies and dysglycemia (i.e., stage 2 T1D) by a median of 2.7 years.

Although other islet cell types (alpha cells [glucagon-producing], delta cells [somatostatin-producing], or PP cells [pancreatic polypeptide-producing]) are functionally and embryologically similar to beta cells, they are spared from the autoimmune destruction. However, altered patterns of hormone secretion from these other cell types in type 1 DM likely contribute to metabolic instability. Alpha cell dysfunction is reflected by fasting and post-prandial hyperglucagonemia but an impaired glucagon response to hypoglycemia.

**Environmental Factors** Numerous environmental events have been proposed to trigger the autoimmune process in genetically susceptible individuals; however, none has been conclusively linked to diabetes. Identification of an environmental trigger has been difficult because the event may precede the onset of DM by several years (Fig. 403-6). Putative environmental triggers include viruses (coxsackie, rubella, enteroviruses most prominently), bovine milk proteins, nitrosourea compounds, vitamin D deficiency, and environmental toxins. There is increasing interest in the microbiome and type 1 diabetes **(Chap. 471)**.

## TYPE 2 DM

Insulin resistance and abnormal insulin secretion are central to the development of type 2 DM. Although the primary defect is controversial, most studies support the view that insulin resistance precedes an insulin secretory defect but that diabetes develops only when insulin secretion becomes inadequate. Type 2 DM likely encompasses a range of disorders with the common phenotype of hyperglycemia. Historically, our understanding of the pathophysiology and genetics is based on studies of individuals of European descent. Studies in more diverse populations have yielded unique insights into pathophysiologic differences among ethnic groups. In general, Latinos have greater insulin resistance and East Asians and South Asians have more beta cell dysfunction, but both defects are present in both populations. East and South Asians appear to develop type 2 DM at a younger age and a lower BMI. In some groups, DM that is ketosis prone (often in obese individuals) or ketosis-resistant (often lean) is sometimes seen. For example, African Americans can be more prone to nonketotic hyperosmolar presentation of diabetes exacerbations. In many forms of type 2 DM, the social determinants of health play a major role in the rates of type 2 DM.

## GENETIC CONSIDERATIONS

Type 2 DM has a strong genetic component. The concordance of type 2 DM in identical twins is between 70% and 90%. Individuals with a parent with type 2 DM have an increased risk of diabetes; if both parents have type 2 DM, the risk approaches 70%. Insulin resistance, as demonstrated by reduced glucose utilization in skeletal muscle, is present in many nondiabetic, first-degree relatives of individuals with type 2 DM. The disease is polygenic and multifactorial, because in addition to genetic susceptibility, environmental factors (such as obesity, poor nutrition, and physical inactivity) modulate the phenotype. Shared environmental and lifestyle factors also contribute to the high concordance in families. Further, the in utero environment contributes to, and either increased or reduced birth weight increases the risk of type 2 DM in adult life. Children of pregnancies complicated by gestational hyperglycemia also exhibit an increased risk of type 2 DM.

The genes that predispose to type 2 DM are incompletely identified, but genome-wide association studies have identified a large number of genes that convey a relatively small risk for type 2 DM (several hundred genes each with a relative risk of 1.06–1.5). Most prominent is a variant of the transcription factor 7-like 2 gene that has been associated with both type 2 DM and IGT in several populations. Genetic polymorphisms associated with type 2 DM have also been found in the genes encoding the peroxisome proliferator–activated receptor γ, inward rectifying potassium channel, zinc transporter, IRS, and calpain 10. The mechanisms by which these genetic loci increase the susceptibility to type 2 DM are not clear, but most are predicted to alter islet function or development or insulin secretion. Although the genetic susceptibility to type 2 DM is under active investigation (it is estimated that <10% of genetic risk is determined by loci identified thus far), it is currently not possible to use a combination of known genetic loci to reliably predict type 2 DM.

**Pathophysiology** Type 2 DM is characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production, abnormal fat metabolism, and systemic low-grade inflammation. Obesity, particularly visceral or central (as evidenced by the hip-waist ratio), is very common in type 2 DM (≥80% of patients are obese). In the early stages of the disorder, glucose tolerance remains near-normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output **(Fig. 403-7)**. A number

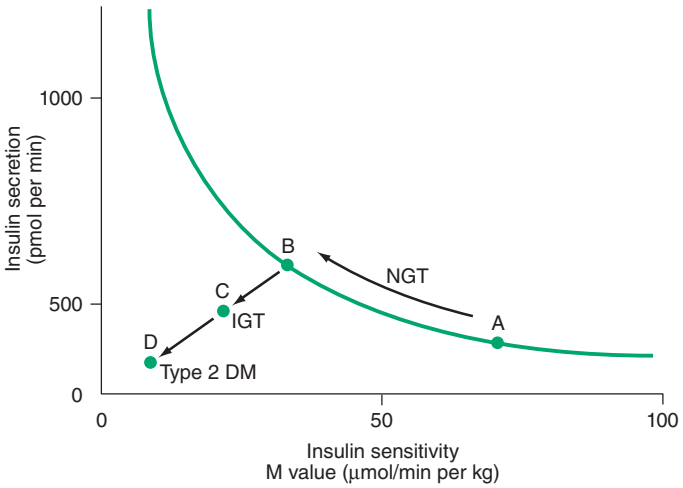


**FIGURE 403-7 Metabolic changes during the development of type 2 diabetes mellitus (DM).** Insulin secretion and insulin sensitivity are related, and as an individual becomes more insulin resistant (by moving from point A to point B), insulin secretion increases. A failure to compensate by increasing the insulin secretion results initially in impaired glucose tolerance (IGT; point C) and ultimately in type 2 DM (point D). NGT, normal glucose tolerance. *(Data from SE Kahn: Clinical review 135: The importance of beta-cell failure in the development and progression of type 2 diabetes. J Clin Endocrinol Metab 86:4047, 2001 and RN Bergman, M Ader: Free fatty acids and pathogenesis of type 2 diabetes mellitus. Trends Endocrinol Metab 11:351, 2000.)*

of pathophysiologic mechanisms contribute to type 2 DM and their relative importance varies from individual to individual. As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state, manifesting as IGT, defined as elevations in postprandial glucose. A decline in insulin secretion and/or increased glucagon secretion causes an increase in hepatic glucose production leading to fasting hyperglycemia. Ultimately, frank beta cell failure ensues as a combination of these mechanisms leading to the manifestation of type 2 diabetes.

**Metabolic Abnormalities** Insulin resistance, the decreased ability of insulin to act effectively on target tissues (especially muscle, liver, and fat), is a prominent feature of type 2 DM and results from a combination of genetic susceptibility, obesity, and metabolic inflammation. Insulin resistance is relative, however, because supranormal levels of circulating insulin will normalize the plasma glucose. In type 2 DM, both insulin potency and efficacy are reduced leading to an overall decrease in glucose utilization under many conditions (30–60% lower than in normal individuals). Insulin resistance impairs glucose utilization by insulin-sensitive tissues (skeletal muscle) and in liver, coupled with elevated glucagon, leads to increased hepatic glucose output. Increased hepatic glucose output predominantly accounts for increased FPG levels, whereas decreased peripheral glucose utilization results in postprandial hyperglycemia.

The precise molecular mechanism leading to insulin resistance in type 2 DM has not been elucidated. Insulin receptor levels and tyrosine kinase activity in skeletal muscle are reduced, but these alterations are most likely secondary to hyperinsulinemia and are not a primary defect. Therefore, "postreceptor" defects in insulin-regulated phosphorylation/dephosphorylation appear to play the predominant role in insulin resistance. Abnormalities include the accumulation of lipid intermediates within skeletal myocytes, which may impair mitochondrial oxidative phosphorylation and reduce insulin-stimulated mitochondrial ATP production. Impaired fatty acid oxidation and lipid accumulation within skeletal myocytes also may generate reactive oxygen species such as lipid peroxides. These and other mechanisms also generate low-grade metabolic inflammation that feeds back and directly worsens insulin resistance. Of note, not all insulin signal transduction pathways are resistant to the effects of insulin (e.g., those controlling cell growth and differentiation using the mitogen-activated protein kinase pathway). Consequently, hyperinsulinemia may increase the insulin action through these pathways, potentially accelerating diabetes-related conditions such as atherosclerosis.

The obesity accompanying type 2 DM, particularly in a central or visceral location, is thought to be part of the pathogenic process (Chap. 401). In addition to these white fat depots, humans have brown fat, which has much greater thermogenic capacity. Efforts are underway to increase the activity or quantity of brown fat. The increased adipocyte mass leads to increased levels of circulating free fatty acids and other fat cell products. For example, adipocytes secrete a number of biologic products (nonesterified free fatty acids, retinol-binding protein 4, leptin, TNF-α, resistin, IL-6, and adiponectin). Further, adipose resident macrophages are an important source of metabolic inflammation in diabetes. In addition to regulating body weight, appetite, and energy expenditure, adipokines also modulate insulin sensitivity. The increased production of free fatty acids and some adipokines may cause insulin resistance in skeletal muscle and liver. The venous drainage of the visceral adipose beds is the portal circulation and this likely contributes to hepatic dysfunction. Free fatty acids also impair glucose utilization in skeletal muscle, promote glucose production by the liver, and impair beta cell function. In contrast, the production by adipocytes of adiponectin, an insulin-sensitizing peptide, is reduced in obesity, and this may contribute to hepatic insulin resistance. Adipocyte products and adipokines also produce an inflammatory state and may explain why markers of inflammation such as IL-6 and C-reactive protein are often elevated in type 2 DM.

**IMPAIRED INSULIN SECRETION** Insulin secretion and sensitivity are interrelated (Fig. 403-7). In type 2 DM, insulin secretion initially increases in response to insulin resistance to maintain normal glucose tolerance. Initially, the insulin secretory defect is mild and selectively involves glucose-stimulated insulin secretion, including a greatly reduced first secretory phase. The response to other nonglucose secretagogues, such as arginine, is preserved, but overall beta cell function is reduced by as much as 50% at the onset of type 2 DM. Abnormalities in proinsulin processing are reflected by increased secretion of proinsulin in type 2 DM. Eventually, the insulin secretory defect is progressive.

The reason(s) for the decline in insulin secretory capacity in type 2 DM is unclear. The assumption is that a second genetic defect—superimposed upon insulin resistance—leads to defects in beta cell function, mass, and potentially cellular identity and differentiation status. Islet amyloid polypeptide or amylin, co-secreted by the beta cell, forms amyloid fibrillar deposits found in the islets of individuals with long-standing type 2 DM. Whether such islet amyloid deposits are a primary or secondary event is not known. The metabolic environment of diabetes also negatively impacts islet function. For example, chronic hyperglycemia paradoxically impairs islet function ("glucose toxicity") and leads to a worsening of hyperglycemia. Improvement in glycemic control is often associated with improved islet function, an important clinical consideration. In addition, elevated levels of free fatty acids ("lipotoxicity"), and systemic and local elevations in pro-inflammatory cytokines from increased numbers of islet-associated macrophages, may also worsen islet function.

**INCREASED HEPATIC GLUCOSE AND LIPID PRODUCTION** In type 2 DM, insulin resistance in the liver reflects the failure of hyperinsulinemia to suppress gluconeogenesis, which results in fasting hyperglycemia and decreased glycogen storage by the liver in the postprandial state. Increased hepatic glucose production occurs early in the course of diabetes, although likely after the onset of insulin and glucagon secretory abnormalities and insulin resistance in skeletal muscle. As a result of insulin resistance in adipose tissue, lipolysis and free fatty acid flux from adipocytes are increased and efficiently cleared by liver leading to increased very-low-density lipoprotein (VLDL)-triglyceride synthesis in hepatocytes and secretion from liver. This is also responsible for the dyslipidemia found in type 2 DM (elevated triglycerides, reduced high-density lipoprotein [HDL], and increased small dense low-density lipoprotein [LDL] particles). If this lipid is retained, steatosis in the liver may lead to nonalcoholic fatty liver disease and abnormal liver function tests.

**Insulin Resistance Syndromes** The insulin resistance condition comprises a spectrum of disorders, with hyperglycemia representing one of the most readily diagnosed features. The *metabolic syndrome*, the *insulin resistance syndrome*, and *syndrome X* are terms used to describe a constellation of metabolic derangements that includes insulin resistance, hypertension, dyslipidemia (decreased HDL and elevated triglycerides), central or visceral obesity, type 2 DM or IGT/IFG, and accelerated cardiovascular disease. This syndrome is discussed in Chap. 408.

A number of relatively rare forms of severe insulin resistance include features of type 2 DM or IGT (Table 403-1). Mutations in the insulin receptor that interfere with binding or signal transduction are a rare cause of insulin resistance. Acanthosis nigricans and signs of hyperandrogenism (hirsutism, acne, and oligomenorrhea in women) are also common physical features. Two distinct syndromes of severe insulin resistance have been described in adults: (1) type A, which affects young women more severely and is characterized by severe hyperinsulinemia, obesity, and features of hyperandrogenism; and (2) type B, which affects middle-aged women and is characterized by severe hyperinsulinemia, features of hyperandrogenism, and autoimmune disorders. Individuals with type A insulin resistance syndrome have an undefined defect in the insulin-signaling pathway; individuals with type B insulin resistance syndrome have autoantibodies directed

at the insulin receptor. These receptor autoantibodies may block insulin binding or may stimulate the insulin receptor, leading to intermittent hypoglycemia.

Polycystic ovary syndrome (PCOS) is a common disorder that affects premenopausal women and is characterized by chronic anovulation and hyperandrogenism **(Chap. 392)**. Insulin resistance is seen in a significant subset of women with PCOS, and the disorder substantially increases the risk for type 2 DM, independent of the effects of obesity.

Lipodystrophies are a group of heterogeneous disorders characterized by selective loss of adipose tissue, leading to severe insulin resistance and hypertriglyceridemia. Lipodystrophies can be inherited or acquired and associated with variable degrees of adipose tissue loss.



**Prevention** Type 2 DM is preceded by a period of IGT or IFG, and a number of lifestyle modifications and pharmacologic agents prevent or delay the onset of DM. Individuals with prediabetes or increased risk of diabetes should be referred to a structured program to reduce body weight and increase physical activity as well as being screened for cardiovascular disease. The Diabetes Prevention Program (DPP) demonstrated that intensive changes in lifestyle (diet and exercise for 30 min/d five times/week) in individuals with IGT prevented or delayed the development of type 2 DM by 58% compared to placebo. This effect was seen in individuals regardless of age, sex, or ethnic group. In the same study, metformin prevented or delayed diabetes by 31% compared to placebo. The lifestyle intervention group lost 5–7% of their body weight during the 3 years of the study; the effects of the intervention persisted for at least 15 years. Studies in Finnish and Chinese populations noted similar efficacy of diet and exercise in preventing or delaying type 2 DM. A number of agents, including α-glucosidase inhibitors, metformin, thiazolidinediones, GLP-1 receptor pathway modifiers, SGLT-2 inhibitors, and orlistat, prevent or delay type 2 DM but are not approved by the U.S. Food and Drug Administration for this purpose. Individuals with a strong family history of type 2 DM and individuals with IFG or IGT should be strongly encouraged to achieve a normal BMI and engage in regular physical activity. Pharmacologic therapy for individuals with prediabetes is currently controversial because its cost-effectiveness and safety profile are not known. The ADA suggests that metformin be considered in individuals with both IFG and IGT who are at very high risk for progression to diabetes (age <60 years, BMI ≥35 kg/m$^2$, and women with a history of GDM). Individuals with IFG, IGT, or an $HbA_{1c}$ of 5.7–6.4% should be monitored annually to determine if diagnostic criteria for diabetes are present.

## GENETICALLY DEFINED, MONOGENIC FORMS OF DM RELATED TO REDUCED INSULIN SECRETION

Several monogenic forms of DM have been identified. Cases of maturity-onset diabetes of the young (MODY) or monogenic diabetes are caused by mutations in genes encoding islet-enriched transcription factors or glucokinase (Fig. 403-5; Table 403-1) and present with an autosomal dominant mode of transmission. MODY 1, MODY 3, and MODY 5 are caused by mutations in hepatocyte nuclear transcription factor (HNF) 4α, HNF-1α, and HNF-1β, respectively. As their names imply, these transcription factors are expressed in the liver but also in other tissues, including the pancreatic islets and kidney. These factors most likely affect islet development, the expression of genes important in glucose-stimulated insulin secretion or the maintenance of beta cell mass. For example, individuals with an HNF-1α mutation (MODY 3) have a progressive decline in glycemic control but may respond to sulfonylureas. In fact, some of these patients were initially thought to have type 1 DM but were later shown to respond to a sulfonylurea, and insulin was discontinued, a major clinical implication. Individuals with an HNF-1β mutation have progressive impairment of insulin secretion and hepatic insulin resistance, and require insulin treatment with minimal response to sulfonylureas. These individuals often have other abnormalities such as renal cysts, mild pancreatic exocrine insufficiency, and abnormal liver function tests. Individuals with MODY 2, the result of mutations in the glucokinase gene, have mild-to-moderate, but stable hyperglycemia that does not respond to oral hypoglycemic agents, and otherwise does not require treatment. Glucokinase catalyzes the formation of glucose-6-phosphate from glucose, a reaction that is important for glucose sensing by the beta cells (Fig. 403-5) and for glucose utilization by the liver. As a result of glucokinase mutations, higher glucose levels are required to elicit insulin secretory responses, thus altering the set point for insulin secretion. MODY 4 is a rare variant caused by mutations in pancreatic and duodenal homeobox 1, a transcription factor that regulates pancreatic development and insulin gene transcription. Homozygous inactivating mutations cause pancreatic agenesis, whereas heterozygous mutations may result in DM. Studies of populations with type 2 DM suggest that mutations in MODY-associated genes are an uncommon (<5%) cause of type 2 DM.

Transient or permanent neonatal diabetes (onset <6 months of age) occurs. Permanent neonatal diabetes is a heterogeneous group of disorders caused by genetic mutations that impact beta cell function and/or pancreatic development (Fig. 403-5). Affected individuals typically require treatment with insulin and exhibit phenotypic overlap with type 1 DM. Activating mutations in the ATP-sensitive potassium channel subunits (Kir6.2 and ABCC8) impair glucose-stimulated insulin secretion. However, these individuals may respond to sulfonylureas and can be treated with these agents. Mutations in the transcription factor *GATA6* are the most common cause of pancreatic agenesis. Homozygous glucokinase mutations cause a severe form of neonatal diabetes, while mutations in mitochondrial DNA are associated with diabetes and deafness. A number of mutations identified in the coding sequence of the insulin gene have been found to interfere with proinsulin folding, processing, and bioactivity and are designated as Mutant *Ins*-gene-induced Diabetes of Youth (MIDYs). Some of the neonatal diabetes syndromes are associated with a spectrum of neurologic dysfunction and a variety of extrapancreatic manifestations. Any individual who developed diabetes at 6 months of age or who has atypical features of type 1 or type 2 diabetes should be screened for forms of monogenic diabetes.

## APPROACH TO THE PATIENT

### Diabetes Mellitus

Once the diagnosis of DM is made, attention should be directed to symptoms related to diabetes (acute and chronic) and classifying the type of diabetes. DM and its complications produce a wide range of symptoms and signs; those secondary to acute hyperglycemia may occur at any stage of the disease, whereas those related to chronic hyperglycemia typically begin to appear during the second decade of hyperglycemia **(Chap. 405)**. Because of long delays in clinical recognition, individuals with previously undetected type 2 DM may present with chronic complications of DM at the time of diagnosis. The history and physical examination should assess for symptoms or signs of acute hyperglycemia and screen for chronic microvascular and macrovascular complications and conditions associated with DM **(Chap. 405)**.

#### HISTORY

A complete medical history should be obtained with special emphasis on DM-relevant aspects such as current weight as well as any recent changes in weight, family history of DM and its complications, sleep history, risk factors for cardiovascular disease, exercise, smoking status, history of pancreatic disease, and ethanol use. Symptoms of hyperglycemia include polyuria, polydipsia, weight loss, fatigue, weakness, blurry vision, frequent superficial infections (vaginitis, fungal skin infections), and slow healing of skin lesions after minor trauma. Metabolic derangements relate mostly to hyperglycemia (osmotic diuresis) and to the catabolic state of the patient (urinary loss of glucose and calories, muscle breakdown due

to protein degradation and decreased protein synthesis). Blurred vision results from changes in the water content of the lens and resolves as hyperglycemia is controlled.

In a patient with established DM, the initial assessment should include a review of symptoms at the time of the initial diabetes diagnosis. This is an essential part of the history that can help define whether the correct type of DM has been diagnosed. Special emphasis should be placed on prior diabetes care, including types of therapies tried, the nature of any intolerance to previous therapies, prior $HbA_{1c}$ levels, self-monitoring blood glucose results, frequency of hypoglycemia (<3.0 mmol/L, <54 mg/dL), presence of DM-specific complications, and assessment of the patient's knowledge about diabetes, exercise, nutrition, and sleep history. Diabetes-related complications may afflict several organ systems, and an individual patient may exhibit some, all, or none of the symptoms related to the complications of DM **(Chap. 405)**. In addition, the presence of DM-related comorbidities should be established (cardiovascular disease, hypertension, dyslipidemia). Pregnancy plans should be ascertained in women of childbearing age. The American Diabetes Association recommends that all women of childbearing age be counseled about the importance of tight glycemic control ($HbA_{1c}$ <6.5%) prior to conception.

### PHYSICAL EXAMINATION

In addition to a complete physical examination, special attention should be given to DM-relevant aspects such as weight and BMI, retinal examination, orthostatic blood pressure, foot examination, peripheral pulses, and insulin injection sites. Depending on other risk factors, a blood pressure >130/80 mmHg or >140/90 mmHg is considered hypertension in individuals with diabetes. Because periodontal disease is more frequent in DM, the teeth and gums should also be examined.

An annual foot examination should (1) assess blood flow (pedal pulses), sensation (vibratory sensation [128-MHz tuning fork at the base of the great toe], the ability to sense touch with a monofilament [5.07, 10-g monofilament]), pinprick sensation, ankle reflexes, and nail care; (2) look for the presence of foot deformities such as hammer or claw toes and Charcot foot; and (3) identify sites of potential ulceration. The ADA recommends annual screening for distal symmetric polyneuropathy beginning with the initial diagnosis of diabetes and annual screening for autonomic neuropathy 5 years after diagnosis of type 1 DM and at the time of diagnosis of type 2 DM. This testing is aimed at detecting loss of protective sensation (LOPS) caused by diabetic neuropathy **(Chap. 405)**.

### CLASSIFICATION OF DM IN AN INDIVIDUAL PATIENT

The etiology of diabetes in an individual with new-onset disease can usually be assigned on the basis of clinical criteria. Individuals with type 1 DM are more likely to have the following characteristics: (1) lean body habitus; (2) requirement of insulin as the initial therapy; (3) propensity to develop ketoacidosis; and (4) a family or personal history of other autoimmune disorders such as autoimmune thyroid disease, adrenal insufficiency, pernicious anemia, celiac disease, and vitiligo. In contrast, individuals with type 2 DM often exhibit the following features: (1) obesity; 80% are obese, but elderly individuals may be lean; (2) may not require insulin therapy initially; and (3) may have associated conditions such as insulin resistance, hypertension, cardiovascular disease, dyslipidemia, or polycystic ovarian syndrome. In type 2 DM, insulin resistance is often associated with abdominal obesity (as opposed to hip and thigh obesity) and hypertriglyceridemia. Although most individuals diagnosed with type 2 DM are older, the age of diagnosis is declining, and there is a marked increase among overweight children and adolescents. Some individuals with phenotypic type 2 DM present with diabetic ketoacidosis but lack autoimmune markers and may be later treated with oral glucose-lowering agents rather than insulin (this clinical picture is sometimes referred to as *ketosis-prone type 2 DM*). On the other hand, some individuals (5–10%) with the phenotypic appearance of type 2 DM do not have absolute insulin deficiency but have autoimmune markers (GAD and other ICA autoantibodies) suggestive of type 1 DM (sometimes termed *latent autoimmune diabetes of the adult*). Such individuals are more likely to require insulin treatment within 5 years. Monogenic forms of diabetes should be considered in those with diabetes onset in childhood or early adulthood and especially those diagnosed within the first 6 months of life, an autosomal pattern of diabetes inheritance, diabetes without typical features of type 1 or 2 diabetes, and stable mild fasting hyperglycemia. Genetic testing should be considered in individuals suspected of having a monogenic form of diabetes as this may guide therapy selection. Despite recent advances in the understanding of the pathogenesis of diabetes, it often remains difficult to categorize some patients unequivocally. Individuals who deviate from the clinical profile of type 1 and type 2 DM, or who have other associated defects such as deafness, pancreatic exocrine disease (type 3c DM), and other endocrine disorders, should be classified accordingly (Table 403-1). A major goal is personalized or precision medicine in the diagnosis and treatment of diabetes.

### LABORATORY ASSESSMENT

The laboratory assessment should first determine whether the patient meets the diagnostic criteria for DM (Fig. 403-1) and then assess the degree of glycemic control **(Chap. 404)**. In addition to the standard laboratory evaluation, the patient should be screened for DM-associated conditions (e.g., albuminuria, dyslipidemia, thyroid dysfunction).

The classification of the type of DM may be facilitated by laboratory assessments. Serum C-peptide measurements may be useful but should always be interpreted with a concurrent blood glucose level. A low C-peptide in the setting of an elevated blood glucose level may confirm a patient's need for insulin. However, C-peptide levels are unable to completely distinguish type 1 from type 2 DM as many individuals with type 1 DM retain some C-peptide production. Measurement of islet cell antibodies at the time of diabetes onset may be useful if the type of DM is not clear based on the characteristics described above.

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# 404 Diabetes Mellitus: Management and Therapies

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## OVERALL GOALS

The goals of therapy for type 1 or type 2 diabetes mellitus (DM) are to (1) eliminate symptoms related to hyperglycemia, (2) reduce or eliminate the long-term microvascular and macrovascular complications of DM (Chap. 405), and (3) allow the patient to achieve as normal a lifestyle as possible. To reach these goals, the physician should identify a target level of glycemic control for each patient, provide the patient with the educational and pharmacologic resources necessary to reach this level, and monitor/treat DM-related complications. Symptoms of diabetes usually resolve when the plasma glucose is <11.1 mmol/L (200 mg/dL), and thus most DM treatment focuses on achieving the second and third goals. This chapter first reviews the ongoing treatment of diabetes in the outpatient setting and then discusses the treatment of severe hyperglycemia, as well as the treatment of diabetes in hospitalized patients.

The care of an individual with either type 1 or type 2 DM requires a multidisciplinary team. Central to the success of this team are the patient's participation, input, and enthusiasm, all of which are essential for optimal diabetes management. Members of the health care team usually include the primary care provider and/or the endocrinologist or diabetologist, a certified diabetes educator, a nutritionist, a psychologist, and possibly a social worker. In addition, when the complications of DM arise, subspecialists (including ophthalmologists, neurologists, podiatrists, nephrologists, cardiologists, and cardiovascular surgeons) with experience in DM-related complications are essential.

## ONGOING ASPECTS OF COMPREHENSIVE DIABETES CARE

A number of names are sometimes applied to different approaches to diabetes care, such as intensive insulin therapy, intensive glycemic control, and "tight control." The current chapter, and other sources, uses the term *comprehensive diabetes care* to emphasize the fact that optimal diabetes therapy involves more than glucose management and medications and is patient-centered and individualized as advocated by the American Diabetes Association (ADA). Although glycemic control is central to optimal diabetes therapy, comprehensive diabetes care of both type 1 and type 2 DM should also detect and manage DM-specific complications (Chap. 405), and modify risk factors for DM-associated diseases. The key elements of comprehensive diabetes care are summarized in Table 404-1. The morbidity and mortality of DM can be greatly reduced by timely and consistent surveillance, including the detection, prevention, and management of DM-related complications (Table 404-1 and Chap. 405). Such screening procedures are indicated for all individuals with DM, but many individuals with diabetes do not receive these or comprehensive diabetes care. In addition to the physical aspects of DM, social, family, financial, cultural, and employment-related issues may impact diabetes care. The treatment goals for patients with diabetes summarized in Table 404-2 should be individualized. The prevention and treatment of clinically significant hypoglycemia (<3.0 mmol/L or 54 mg/dL) is discussed in Chap. 406. This chapter, while recognizing that resources available for diabetes care vary widely throughout the world, provides guidance for comprehensive diabetes care in health care settings with considerable societal resources.

**Lifestyle Management in Diabetes Care** The patient with type 1 or type 2 DM should receive education about nutrition, physical activity, psychosocial support, care of diabetes during illness, and medications to lower the plasma glucose. Patient education allows and encourages individuals with DM to assume greater responsibility for their care, leading to improved compliance.

**TABLE 404-1 Guidelines for Ongoing, Comprehensive Medical Care for Individuals with Diabetes**

- Individualized glycemic goal and therapeutic plan
- Self-monitoring at individualized frequency of blood glucose (capillary/meter) or interstitial glucose (continuous glucose monitoring)
- $HbA_{1c}$ testing (2–4 times/year)
- Lifestyle management in the care of diabetes, including:
  - Diabetes self-management education and support
  - Nutrition therapy
  - Physical activity
  - Psychosocial care, including evaluation for depression, anxiety
- Detection, prevention, or management of diabetes-related complications, including:
  - Diabetes-related eye examination (annual or biannual; Chap. 405)
  - Diabetes-related foot examination (1–2 times/year by provider; daily by patient; Chap. 403)
  - Diabetes-related neuropathy examination (annual; Chap. 403)
  - Diabetes-related kidney disease testing (annual; Chap. 405)
- Manage or treat diabetes-relevant conditions, including:
  - Blood pressure (assess 2–4 times/year; Chap. 405)
  - Lipids (1–2 times/year; Chap. 405)
  - Consider antiplatelet therapy with low-dose aspirin (Chap. 405)
  - Influenza/pneumococcal/hepatitis B/coronavirus immunizations (Chap. 6)

*Abbreviation:* $HbA_{1c}$, glycosylated hemoglobin $A_{1c}$.

**Diabetes Self-Management Education and Support (DSMES)** DSMES refers to ways to improve the patient's knowledge, skills, and abilities necessary for diabetes self-care and should also emphasize psychosocial issues and emotional well-being. Patient education is a continuing process with regular visits for reinforcement; it is not a process completed after one or two visits. It should receive special emphasis at the diagnosis of diabetes, annually, or at times when diabetes treatment goals are not attained, and during transitions in life or medical care. DSMES is delivered by a diabetes educator who is a health care professional (nurse, dietician, or pharmacist) with specialized patient-education skills and who is certified in diabetes education (e.g., Association of Diabetes Care & Education Specialists). Education topics important for optimal diabetes self-care include self-monitoring of blood glucose (SMBG) and/or continuous glucose monitoring (CGM); urine or blood ketone monitoring (type 1 DM); insulin administration; guidelines for diabetes management during illnesses;

**TABLE 404-2 Treatment Goals for Adults with Diabetes[a]**

| INDEX OF GLYCEMIC CONTROL[b] | GOAL (NONPREGNANT ADULTS) | GOAL (OLDER/HIGH-RISK ADULTS) |
|---|---|---|
| $HbA_{1c}$ | <7.0% (53 mmol/mol)[c] | <8.0% (64 mmol/mol)[c] |
| Preprandial capillary blood glucose | 4.4–7.2 mmol/L (80–130 mg/dL) | 5.0–7.8 mmol/L (90–140 mg/dL) |
| Postprandial capillary blood glucose[d] | <10.0 mmol/L (<180 mg/dL) | <11.1 mmol/L (200 mg/dL) |
| Time in range 3.9–10.0 mmol/L (70–180 mg/dL)[e] | >70% | >50% |
| Time below 3.9 mmol/L (70 mg/dL)[e] | <4% | <1% |
| Glucose variability, % coefficient of variation[e] | ≤36% | <33% |

[a]As recommended by the American Diabetes Association; goals should be individualized for each patient (see text) with personalized goals for different patients. [b]$HbA_{1c}$ is primary goal and may also be estimated from 14 or more days of continuous glucose monitoring (CGM) data as the Glycemic Management Indicator (GMI). [c]Diabetes Control and Complications Trial-based assay. [d]1–2 h after beginning of a meal. [e]Derived from 14 days of CGM data.

*Abbreviation:* $HbA_{1c}$, glycosylated hemoglobin $A_{1c}$.

*Source:* Data from American Diabetes Association: 6. Glycemic targets: Standards of medical care in diabetes-2021. Diabetes Care 44(Suppl 1):S73, 2021.

prevention and management of hypoglycemia (Chap. 406); foot and skin care; diabetes management before, during, and after exercise; and risk factor–modifying activities. The focus is providing patient-centered, individualized education. More frequent contact between the patient and the diabetes management team (e.g., electronic, telephone, video) improves glycemic control.

**Nutrition Therapy** *Medical nutrition therapy* (MNT) is a term used by the ADA to describe the optimal coordination of caloric intake with other aspects of diabetes therapy (insulin, exercise, and weight loss). Some aspects of MNT are directed at preventing or delaying the onset of type 2 DM in high-risk individuals (obese or with prediabetes) by promoting weight reduction. Other measures of MNT are directed at improving glycemic control through limiting carbohydrate intake and avoiding simple sugars and fructose and managing diabetes-related complications (cardiovascular disease [CVD], nephropathy). Medical treatment of obesity including pharmacologic approaches that facilitate weight loss and metabolic surgery should be considered in selected patients (Chaps. 401 and 402).

In general, the components of optimal MNT are similar for individuals with type 1 or type 2 DM—high-quality, nutrient-dense with limits on carbohydrate intake required for glycemic control and weight management (Table 404-3). The data are currently inconclusive about various eating patterns (intermittent fasting, etc.). Dietary advice should be individualized, acknowledging personal preferences, culture, and religious traditions. Using the *glycemic index*, an estimate of the postprandial rise in the blood glucose when a certain amount of that food is consumed, may reduce postprandial glucose excursions and improve glycemic control.

The goal of MNT in type 1 DM is to coordinate and match the carbohydrate intake, both temporally and quantitatively, with the appropriate amount of insulin. MNT in type 1 DM is informed by SMBG and/or CGM that should be integrated to define the optimal insulin regimen. Based on the patient's estimate of the carbohydrate content of a meal, an insulin-to-carbohydrate ratio determines the bolus insulin dose for a meal or snack. MNT must be flexible enough to allow for exercise, and the insulin regimen must allow for variations in caloric intake. An important component of MNT in type 1 DM is to minimize the weight gain often associated with intensive insulin therapy and is best achieved by placing limits on carbohydrate intake.

The goals of MNT in type 2 DM should focus on weight loss and address the greatly increased prevalence of cardiovascular risk factors (hypertension, dyslipidemia, obesity) and disease in this population. The majority of these individuals are obese, and weight loss is strongly encouraged. Very-low-carbohydrate diets that induce weight loss may result in rapid and dramatic glucose lowering in individuals with new-onset type 2 DM. MNT for type 2 DM should emphasize modest caloric reduction, increased physical activity, and weight loss (goal of at least 5–10% loss). Weight loss and exercise each independently improve insulin sensitivity.

Fasting for religious reasons, such as during Ramadan, presents a challenge for individuals with diabetes, especially those taking medications to lower the plasma glucose. Under International Diabetes Federation (IDF) guidelines on fasting during Ramadan, individuals are risk-stratified as those who can safely fast with medical evaluation and supervision and those in whom fasting is not advised. Thus, patient education and regular glucose monitoring are critical.

**TABLE 404-3 Nutritional Recommendations for Adults with Diabetes or Prediabetes[a]**

**General dietary guidelines**

- Vegetable, fruits, whole grains, legumes, low-fat dairy products and food higher in fiber and lower in glycemic content; optimal diet composition and eating pattens are not known

**Fat in diet** (optimal % of diet is not known; should be individualized)

- Mediterranean-style diet rich in monounsaturated and polyunsaturated fatty acids
- Minimal or no trans fat consumption

**Carbohydrate in diet** (optimal % of diet is not known; should be individualized)

- Monitor carbohydrate intake in regard to calories and set limits for meals to reduce postprandial glycemia
- Avoid fructose- and sucrose-containing beverages and minimize consumption of foods with added sugar that may displace healthier, more nutrient-dense food choices and elevate postprandial glycemia
- Estimate grams of carbohydrate in diet for flexible insulin dosing (type 1 DM and insulin-dependent type 2 DM)
- Consider using glycemic index to predict how consumption of a particular food may affect blood glucose

**Protein in diet** (optimal % of diet is not known; should be individualized)

**Other components**

- Reduced-calorie and nonnutritive sweeteners may be useful
- Routine supplements of vitamins, antioxidants, or trace elements not supported by evidence
- Sodium intake as advised for general population

[a]See text for differences for patients with type 1 or type 2 diabetes.

*Source:* Data from American Diabetes Association: 5. Facilitating behavior change and well-being to improve health outcomes: Standards of medical care in diabetes-2021. Diabetes Care 44(Suppl 1):S53, 2021.

**Physical Activity** Exercise has multiple positive benefits including cardiovascular risk reduction, reduced blood pressure, maintenance of muscle mass, reduction in body fat, and weight loss. For individuals with type 1 or type 2 DM, exercise is also useful for lowering plasma glucose (during and following exercise) and increasing insulin sensitivity. In patients with diabetes, the ADA recommends 150 min/week (distributed over at least 3 days) of moderate aerobic physical activity with no gaps longer than 2 days. Resistance exercise, flexibility and balance training, and reduced sedentary behavior throughout the day are advised.

Despite its benefits, exercise may present challenges for some individuals with DM because they lack the normal glucoregulatory mechanisms (normally, insulin falls and glucagon rises during exercise). Skeletal muscle is a major site for metabolic fuel consumption in the resting state, and the increased muscle activity during vigorous, aerobic exercise greatly increases fuel requirements. Individuals with type 1 DM are prone to either hyperglycemia or hypoglycemia during exercise, depending on the preexercise plasma glucose, the circulating insulin level, lactate, and the level of exercise-induced catecholamines. If the insulin level is too low, the delivery of lactate to the liver and rise in catecholamines may increase the plasma glucose excessively, promote ketone body formation, and possibly lead to ketoacidosis. Conversely, if the circulating insulin level is excessive, this relative hyperinsulinemia may reduce hepatic glucose production (decreased glycogenolysis, decreased gluconeogenesis) and increase glucose entry into muscle, leading to hypoglycemia.

To avoid exercise-related hyper- or hypoglycemia, individuals with type 1 DM should (1) monitor blood glucose before, during, and after exercise; (2) delay exercise if blood glucose is >14 mmol/L (250 mg/dL) and ketones are present; (3) if the blood glucose is <5.0 mmol/L (90 mg/dL), ingest carbohydrate before exercising; (4) monitor glucose during exercise and ingest carbohydrate as needed to prevent hypoglycemia; (5) decrease insulin doses (based on previous experience) before and after exercise and inject insulin into a nonexercising area; and (6) learn individual glucose responses to different types of exercise. In individuals with type 2 DM, exercise-related hypoglycemia is less common but can occur in individuals taking either insulin or insulin secretagogues. Untreated proliferative retinopathy is a relative contraindication to vigorous exercise, because this may lead to vitreous hemorrhage or retinal detachment (Chap. 405).

**Psychosocial Care** Because the individual with DM faces challenges that affect many aspects of daily life, psychosocial assessment and support are a critical part of comprehensive diabetes care. The patient should view himself/herself as an essential member of the diabetes care team and not as someone who is cared for by the diabetes management team. Even with considerable effort, normoglycemia can be an elusive goal, and solutions to worsening glycemic control may not be easily identifiable. Depression, anxiety, or "diabetes distress," defined by the ADA as "…negative psychological reactions related to

emotional burdens…in having to manage a chronic disease like diabetes," should be recognized and may require the care of a mental health specialist. Emotional stress may provoke a change in behavior so that individuals no longer adhere to a dietary, exercise, or therapeutic regimen. Eating disorders, including binge eating disorders, bulimia, and anorexia nervosa, appear to occur more frequently in individuals with type 1 or type 2 DM.

## MONITORING THE LEVEL OF GLYCEMIC CONTROL

Optimal monitoring of glycemic control involves glucose measurements by the patient and an assessment of long-term control by the providers on the diabetes management team (measurement of hemoglobin $A_{1c}$ [$HbA_{1c}$] and review of the patient's SMBG and/or CGM). These measurements are complementary: the patient's measurements provide a picture of short-term glycemic control, whereas the $HbA_{1c}$ reflects average glycemic control over the previous 2–3 months. Most measurements should be performed prior to a meal and supplemented with postprandial measurements to assist in reaching glucose targets (Table 404-2). By combining glucose measurements with diet and exercise history, the diabetes management team and patient can improve glycemic control. Clinical practice is changing rapidly with CGM replacing SMBG is many patients, especially those with T1 DM.

**Self-Monitoring of Blood Glucose** In SMBG, a small drop of blood (3–10 μL) and an enzymatic reaction allow rapid and accurate measurement of the capillary blood glucose by glucose monitors (calibrated to provide plasma glucose value even though blood glucose is measured). The blood is obtained from the fingertip; alternative testing sites (e.g., forearm) are less reliable. The frequency of SMBG measurements should be individualized. Individuals with type 1 DM or individuals with type 2 DM taking multiple insulin injections each day should measure their blood glucose >3 times/day (some measure >10 times/day). Most individuals with type 2 DM require less frequent monitoring, although the optimal frequency of SMBG has not been clearly defined. Individuals with type 2 DM who are taking insulin should use SMBG more frequently than those on oral agents. Individuals with type 2 DM who are on oral medications should use SMBG as a means of assessing the efficacy of their medication and the impact of dietary choices and exercise. Because glucose levels fluctuate less in these individuals, one or two SMBG measurements per day may be sufficient.

**Continuous Glucose Monitoring** CGM technology utilizes a sensor or electrode to detect interstitial glucose, which is in equilibrium with blood glucose, but may lag behind when the blood glucose is changing. In one CGM approach, the interstitial glucose is detected and reported essentially continuously while in another approach, the sensor is in place, but the glucose is only recorded when a detector is placed over the sensor. The glucose sensors are placed subcutaneously and are replaced every 3–14 days. Some CGM requires calibration by SMBG. CGM provides unlimited glucose datapoints that can be used to define a time in a glycemic range (TIR, or time in range), the ambulatory glucose profile, the amount of time in the hypoglycemic range, and the glucose management indicator (GMI), which correlates with A1C **(Fig. 404-1; Table 404-2)**. TIR and GMI are useful metrics but CGM also allows the patient to monitor the rate of glucose change and glucose trends that can be used to avoid predicted hyper- or hypoglycemia. CGM in type 1 DM especially in those with hypoglycemia unawareness can decrease the frequency of serious hypoglycemia (especially nocturnal hypoglycemia). The combination of an insulin-infusion device (discussed below) and a CGM can now automate insulin delivery with either predictive suspension of insulin delivery to avoid hypoglycemia or closed-loop control that automatically adjusts insulin delivery by a predictive algorithm (Fig. 404-1).

**Assessment of Long-Term Glycemic Control** Measurement of glycated hemoglobin ($HbA_{1c}$) is the standard method for assessing long-term glycemic control. When plasma glucose is consistently elevated, there is an increase in nonenzymatic glycation of hemoglobin; this alteration reflects the glycemic history over the previous 2–3 months, because erythrocytes have an average life span of 120 days (glycemic

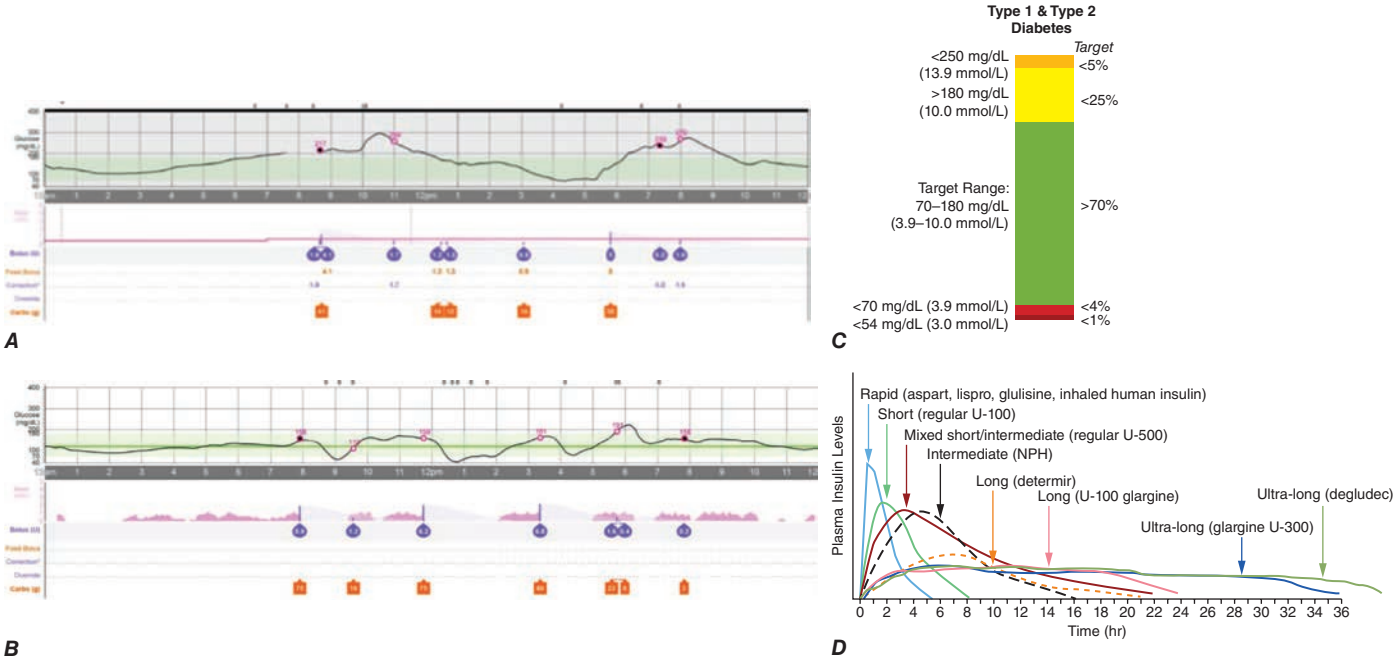


**FIGURE 404-1 Glycemic monitoring and insulin administration options for treatment of diabetes.** ***A.*** CGM profile and delivery of rapid-acting insulin analog by continuous subcutaneous insulin infusion pump involves a basal rate (*light purple line*) and prandial and correction boluses (*purple circles*) based on estimated carbohydrate intake (*orange squares*) and an insulin sensitivity factor. ***B.*** CGM profile with sensor-communicating insulin pump that automates insulin delivery by suspending delivery for predicted hypoglycemia and increasing basal delivery for predicted hyperglycemia (*light purple curves*) while still requiring user input for estimated carbohydrate intake (*orange squares*) to provide prandial insulin boluses (*purple circles*). ***C.*** CGM profile is used to generate an estimate of time-in-range with glycemic goal shown on the left side of the bar and target % time in that glycemic range shown on the right side of the bar. ***D.*** Pharmacokinetic profile of individual insulin products. ***(C.*** *Reproduced with permission from T Battelino et al: Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the International Consensus on Time in Range. Diabetes Care 42:1593, 2019;* ***D.*** *Adapted with permission from JJ Neumiller: Insulin update: New and emerging insulins. American Diabetes Association, 2018.)*

level in the preceding month contributes about 50% to the $HbA_{1c}$ value). Measurement of $HbA_{1c}$ at the "point of care" allows for more rapid feedback and may therefore assist in adjustment of therapy.

$HbA_{1c}$ should be measured in all individuals with DM during their initial evaluation and as part of their comprehensive diabetes care. As the primary predictor of long-term complications of DM, the $HbA_{1c}$ should mirror, to a certain extent, the short-term measurement by SMBG or CGM. Measurements of $HbA_{1c}$ and actual glucose levels are complementary in that recent intercurrent illnesses may impact SMBG or CGM measurements but not the $HbA_{1c}$. The $HbA_{1c}$ may reflect postprandial or nocturnal hyperglycemia not detected by SMBG of fasting and preprandial capillary blood glucose. However, it does not detect interprandial or nocturnal hypoglycemia—these require very frequent SMBG or CGM for detection. The $HbA_{1c}$ is an "average" and thus does not detect glycemic variability in the way SMBG and CGM can. In standardized assays, the $HbA_{1c}$ approximates the following mean plasma glucose values: an $HbA_{1c}$ of 6% = 7.0 mmol/L (126 mg/dL), 7% = 8.6 mmol/L (154 mg/dL), 8% = 10.2 mmol/L (183 mg/dL), 9% = 11.8 mmol/L (212 mg/dL), 10% = 13.4 mmol/L (240 mg/dL), 11% = 14.9 mmol/L (269 mg/dL), and 12% = 16.5 mmol/L (298 mg/dL). However, there is interindividual variability in the $HbA_{1c}$ to mean glucose relationship, and in blacks the $HbA_{1c}$ is on average 0.4% higher than in whites for the same mean glucose. Clinical conditions leading to abnormal RBC parameters such as hemoglobinopathies, anemias, reticulocytosis, transfusions, and uremia may alter the $HbA_{1c}$ result. In patients achieving their glycemic goal, the ADA recommends measurement of the $HbA_{1c}$ at least twice per year. More frequent testing (every 3 months) is warranted when glycemic control is inadequate or when therapy has changed. Laboratory standards for the $HbA_{1c}$ test have been established and should be correlated to the reference assay of the Diabetes Control and Complications Trial (DCCT). The degree of glycation of other proteins, such as albumin, or measurement of 1,5-anhydroglucitol can be used as an alternative, shorter-term indicator of glycemic control when the $HbA_{1c}$ is inaccurate. The fructosamine assay (measuring glycated albumin) reflects the glycemic status over the prior 2 weeks.

## PHARMACOLOGIC TREATMENT OF DIABETES

Comprehensive care of type 1 and type 2 DM requires an emphasis on nutrition, exercise, and monitoring of glycemic control but also usually involves glucose-lowering medication(s). This chapter discusses classes of such medications but does not describe every glucose-lowering agent available worldwide. The initial step is to select an individualized, glycemic goal for the patient.

### ESTABLISHMENT OF TARGET LEVEL OF GLYCEMIC CONTROL

Because the complications of DM are related to glycemic control, normoglycemia or near-normoglycemia is the desired, but often elusive, goal for most patients. Normalization or near-normalization of the plasma glucose for long periods of time is extremely difficult, as demonstrated by the DCCT and United Kingdom Prospective Diabetes Study (UKPDS). Regardless of the level of hyperglycemia, improvement in glycemic control will lower the risk of diabetes-specific complications, most notably the microvascular complications **(Chap. 405)**.

The target for glycemic control (as reflected by the $HbA_{1c}$) must be individualized, and the goals of therapy should be developed in consultation with the patient after considering a number of medical, social, and lifestyle issues. The ADA calls this a *patient-centered approach*, and other organizations such as the IDF and American Association of Clinical Endocrinologists (AACE) also suggest an individualized glycemic goal. Important factors to consider include the patient's age and ability to understand and implement a complex treatment regimen, presence and severity of complications of diabetes, known CVD, ability to recognize hypoglycemic symptoms, presence of other medical conditions or treatments that might affect survival or the response to therapy, lifestyle and occupation (e.g., possible consequences of experiencing hypoglycemia on the job), and level of support available from family and friends.

In general, the ADA suggests that the goal is to achieve an $HbA_{1c}$ as close to normal as possible without significant hypoglycemia. In most individuals, the target $HbA_{1c}$ should be <7% (Table 404-2) with a more stringent (≤6.5%) target for some patients. With modern implementation of intensive insulin therapy for type 1 DM, the level of $HbA_{1c}$ is no longer inversely related to the frequency and severity of hypoglycemia as seen in the DCCT; nevertheless, it may still be appropriate to set a higher $HbA_{1c}$ target <7.5 or 8% for patients with impaired awareness of hypoglycemia. A higher $HbA_{1c}$ goal may also be appropriate for the very young or old or in individuals with limited life span or comorbid conditions. For individuals using CGM, maximizing time-in-range 70–180 mg/dL, representing normoglycemia, while minimizing time-below-range <70 mg/dL, representing hypoglycemia, are shorter-term targets of therapy.

More stringent glycemic control ($HbA_{1c}$ ≤6%) is not beneficial, and may be detrimental, in patients with type 2 DM and a high risk of CVD. Large clinical trials (UKPDS, Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], Veterans Affairs Diabetes Trial [VADT]; **Chap. 405**) examined glycemic control in type 2 DM in individuals with low risk of CVD, with high risk of CVD, or with established CVD and have found that more intense glycemic control is not beneficial and, in some patient populations, may have a negative impact on some outcomes. These divergent outcomes stress the need for individualized glycemic goals based on the following general guidelines: (1) early in the course of type 2 diabetes when the CVD risk is lower, improved glycemic control likely leads to improved cardiovascular outcome, but this benefit may occur more than a decade after the period of improved glycemic control; (2) intense glycemic control in individuals with established CVD or at high risk for CVD is not advantageous, and may be deleterious, over a follow-up of 3–5 years; (3) hypoglycemia in such high-risk populations (elderly, CVD) should be avoided; and (4) improved glycemic control reduces microvascular complications of diabetes **(Chap. 405)** even if it does not improve macrovascular complications like CVD.

### TYPE 1 DIABETES MELLITUS

**General Aspects** The ADA recommendations for glycemic goals and $HbA_{1c}$ targets are summarized in Table 404-2. The goal is to design and implement insulin regimens that mimic physiologic insulin secretion. Because individuals with type 1 DM partially or completely lack endogenous insulin production, administration of basal insulin is essential for regulating glycogen breakdown, gluconeogenesis, lipolysis, and ketogenesis (i.e., largely fine-tuning hepatic and adipose metabolism). Likewise, insulin replacement for meals should be appropriate for the carbohydrate intake and insulin sensitivity, promoting normal glucose utilization and storage.

**Intensive Management** Intensive insulin therapy has the goal of achieving near-normal glycemia. This approach requires multiple resources, including thorough and continuing patient education, comprehensive recording of plasma glucose measurements and nutrition intake by the patient, and a variable insulin regimen that matches carbohydrate intake and insulin dose. Insulin regimens include multiple-component insulin regimens, multiple daily injections (MDIs), or continuous subcutaneous (SC) insulin infusion (CSII).

The benefits of intensive insulin therapy and improved glycemic control include a reduction in the acute metabolic and chronic microvascular complications of DM. From a psychological standpoint, the patient experiences greater control over his or her diabetes and often notes an improved sense of well-being, greater flexibility in the timing and content of meals, and the capability to alter insulin dosing with exercise. In addition, intensive insulin therapy prior to and during pregnancy reduces the risk of fetal malformations and morbidity. Intensive insulin therapy is encouraged in newly diagnosed patients with type 1 DM because it may prolong the period of C-peptide production, which may result in better glycemic control and a reduced risk of serious hypoglycemia. Although intensive management confers impressive benefits, it is also accompanied by significant personal and financial costs and therefore may not be appropriate at all times for all individuals.

**TABLE 404-4 Properties of Insulin Preparations[a]**

| PREPARATION | TIME OF ACTION | | |
|---|---|---|---|
| | ONSET, h | PEAK, h | EFFECTIVE DURATION, h |
| **Short-acting** | | | |
| Aspart[b] | <0.25 | 0.5–1.5 | 3–5 |
| Glulisine | <0.25 | 0.5–1.5 | 3–5 |
| Lispro[c] | <0.25 | 0.5–1.5 | 3–5 |
| Regular[d] | 0.5–1.0 | 2–3 | 4–8 |
| Inhaled human insulin | <0.5 | 1–2 | 3 |
| **Long-acting** | | | |
| Degludec | 1–9 | —[e] | 42[f] |
| Detemir | 1–4 | —[e] | 12–24[f] |
| Glargine[g] | 2–4 | —[e] | 20–24 |
| NPH | 2–4 | 4–10 | 10–16 |
| **Examples of insulin combinations[h]** | | | |
| 75/25–75% protamine lispro, 25% lispro | <0.25 | Dual[i] | 10–16 |
| 70/30–70% protamine aspart, 30% aspart | <0.25 | Dual[i] | 15–18 |
| 50/50–50% protamine lispro, 50% lispro | <0.25 | Dual[i] | 10–16 |
| 70/30–70% NPH, 30% regular | 0.5–1 | Dual[i] | 10–16 |
| Combination of long-acting insulin and GLP-1 receptor agonist | See text | | |

[a]Injectable insulin preparations (with exception of inhaled formulation) available in the United States; others are available in the United Kingdom and Europe. Standard formulations are U-100 (100 units of insulin per mL solution). [b]Formulation with niacinamide (vitamin B3) has a slightly more rapid onset and offset. [c]Lispro-aabc formulation has a slightly more rapid onset and offset; both formulations are also available in U-200 concentration. [d]Formulation also available in U-500 concentration with delayed onset and offset. [e]Degludec, determir, and glargine have minimal peak activity. [f]Duration is dose-dependent. [g]Formulation also available in U-300 concentration with delayed onset and offset. [h]Other insulin combinations are available. [i]Dual: two peaks—one at 2–3 h and the second one several hours later.

**Insulin Preparations** Current insulin preparations are generated by recombinant DNA technology and consist of the amino acid sequence of human insulin or variations thereof. In the United States, most insulin is formulated as U-100 (100 units/mL); short-acting insulin formulated as U-200 (200 units/mL; lispro) and long-acting as U-300 (300 units/mL; glargine) are available in order to limit injection volumes for patients with high insulin requirements. Regular insulin formulated as U-500 (500 units/mL) is sometimes used in patients with severe insulin resistance. Human insulin has been formulated with distinctive pharmacokinetics (regular and neutral protamine Hagedorn [NPH] insulin have the native insulin amino acid sequence) or genetically modified to alter insulin absorption and hence insulin action. Insulins can be classified as short-acting or long-acting **(Table 404-4; Figure 404-1D)**. For example, one short-acting insulin formulation, insulin lispro, is an insulin analogue in which the 28th and 29th amino acids (lysine and proline) on the insulin B chain have been reversed by recombinant DNA technology. Insulin aspart and insulin glulisine are genetically modified insulin analogues with properties similar to lispro. A biosimilar version of lispro has been approved. These insulin analogues have full biologic activity but less tendency for self-aggregation, resulting in more rapid absorption and onset of action and a shorter duration of action. These characteristics are particularly advantageous for allowing entrainment of insulin injection and action to rising plasma glucose levels following meals. The shorter duration of action also appears to be associated with a decreased number of hypoglycemic episodes, primarily because the decay of insulin action corresponds to the decline in plasma glucose after a meal. Thus, insulin aspart, lispro, or glulisine is preferred over regular insulin for prandial coverage in many patients. Insulin glargine is a long-acting biosynthetic human insulin that differs from normal insulin in that asparagine is replaced by glycine at amino acid 21, and two arginine residues are added to the C terminus of the B chain, leading to the formation of microprecipitates at physiologic pH in subcutaneous tissue. Compared to NPH insulin, the onset of insulin glargine action is later, the duration of action is longer (~24 h), and there is a less pronounced peak. A lower incidence of hypoglycemia, especially at night, has been reported with insulin glargine when compared to NPH insulin. A biosimilar version is available. Insulin detemir has a fatty acid side chain that reversibly binds to albumin and prolongs its action by slowing absorption and catabolism, but its duration of action may only reach 12–20 h. Twice-daily injections of glargine, or especially detemir, are sometimes required to provide optimal 24-h basal insulin coverage. Because of modification and extension of the carboxy-terminus of the B chain, insulin degludec forms multihexamers in subcutaneous tissue and binds albumin, prolonging its duration of action (>42 h); it provides similar glycemic control as glargine but with less frequent nocturnal and severe hypoglycemia. Other modified insulins, such as one with a duration of action of several days, are in development.

Basal insulin requirements are provided by long-acting insulin formulations (NPH insulin, insulin glargine, insulin detemir, or insulin degludec) (Fig. 404-1D; Table 404-4). These are usually prescribed with short-acting insulin in an attempt to mimic physiologic insulin release with meals. Although mixing of NPH and short-acting insulin formulations is common practice, this mixing may alter the insulin absorption profile (especially the short-acting insulins). For example, lispro absorption is delayed by mixing with NPH. The alteration in insulin absorption when the patient mixes different insulin formulations should not prevent mixing insulins. However, the following guidelines should be followed: (1) mix the different insulin formulations in the syringe immediately before injection (inject within 2 min after mixing); (2) do not store insulin as a mixture; (3) follow the same routine in terms of insulin mixing and administration to standardize the physiologic response to injected insulin; and (4) do not mix insulin glargine, detemir, or degludec with other insulins. The miscibility of some insulins allows for the production of combination insulins that contain 70% NPH and 30% regular (70/30), or equal mixtures of NPH and regular (50/50). By including the insulin analogue mixed with protamine, several additional combinations have a short-acting and long-acting profile (Table 404-4; Fig. 404-1D). Although more convenient for the patient (only two injections/day), combination insulin formulations do not allow independent adjustment of short-acting and long-acting activity. Several insulin formulations are available as insulin "pens," which are more convenient for some patients. Insulin delivery by inhalation to provide meal-time insulin is approved, but not widely used. Prior to its use, the forced expiratory volume in 1 second ($FEV_1$) should be measured. Inhaled insulin can cause bronchospasm and cough and should not be used by individuals with lung disease or those who smoke. Long-acting insulin/glucagon-like peptide-1 (GLP-1) receptor agonist combinations in fixed doses (degludec + liraglutide or glargine + lixisenatide) are effective, and are associated with less weight gain.

**Insulin Regimens** There is considerable patient-to-patient variation in the peak and duration. In all regimens, long-acting insulins (NPH, glargine, detemir, or degludec) supply basal insulin, whereas regular, insulin aspart, glulisine, or lispro provide prandial insulin (Fig. 404-1D; Table 404-4). Short-acting insulin analogues should be injected just before (<10 min) and regular insulin 30–45 min prior to a meal. Sometimes short-acting insulin analogues are injected just after a meal (gastroparesis, unpredictable food intake).

A shortcoming of current insulin regimens is that injected insulin immediately enters the systemic circulation, whereas endogenous insulin is secreted into the portal venous system. Thus, exogenous insulin administration exposes the liver to subphysiologic insulin levels. No current insulin regimen reproduces the precise insulin secretory pattern of the pancreatic islet. However, the most physiologic regimens entail more frequent insulin injections, greater reliance on short-acting insulin, and more frequent SMBG and/or CGM. In general, individuals with type 1 DM require 0.3-0.7 units/kg per day of insulin divided into

multiple doses, with approximately 50% of daily insulin given as basal insulin and 50% as prandial insulin.

MDI regimens refer to the combination of basal insulin and bolus insulin (preprandial short-acting insulin). The timing and dose of short-acting, preprandial insulin are altered to accommodate the SMBG or CGM results, anticipated food intake, and physical activity. Such regimens offer the patient with type 1 DM more flexibility in terms of lifestyle and the best chance for achieving near normoglycemia. Most often basal insulin with glargine, detemir, or degludec is used in conjunction with preprandial lispro, glulisine, or insulin aspart. The insulin aspart, glulisine, or lispro dose is based on individualized algorithms that integrate the preprandial glucose and the anticipated carbohydrate intake. To determine the meal component of the preprandial insulin dose, the patient uses an insulin-to-carbohydrate ratio (a common ratio for type 1 DM is 1 unit/10–15 g of carbohydrate, but this must be determined for each individual). To this insulin dose is added the supplemental or correcting insulin based on the preprandial blood glucose (one formula uses 1 unit of insulin for every 1.6–3.3 mmol/L [30–60 mg/dL] over the preprandial glucose target; this correction factor can be estimated from 1500/[total daily insulin dose]). Such calculations must be adjusted based on each individual's sensitivity to insulin. Other variations of this regimen use twice daily NPH as basal insulin but have the disadvantage that NPH has a significant peak, making hypoglycemia more common. Frequent SMBG (≥4 times per day) or CGM is essential for these types of insulin regimens.

CSII is a very effective insulin regimen for the patient with type 1 DM (Fig. 404-1). To the basal insulin infusion, a preprandial insulin ("bolus") is delivered by the insulin infusion device based on instructions from the patient, who uses an individualized algorithm incorporating the preprandial plasma glucose and anticipated carbohydrate intake. These sophisticated devices can accurately deliver small doses of insulin (microliters per hour) and have several advantages: (1) multiple basal infusion rates can be programmed to accommodate nocturnal versus daytime basal insulin requirement; (2) basal infusion rates can be altered during periods of exercise; (3) different waveforms of insulin infusion with meal-related bolus allow better matching of insulin depending on meal composition; and (4) programmed algorithms consider ongoing action of prior insulin administration and blood glucose values in calculating the insulin dose. These devices require instruction by a health professional with considerable experience with insulin infusion devices and frequent patient interactions with the diabetes management team. Insulin infusion devices may present unique challenges, such as infection at the infusion site, unexplained hyperglycemia because the infusion set becomes obstructed, or diabetic ketoacidosis (DKA) if the insulin infusion device becomes disconnected. Because most physicians use lispro, glulisine, or insulin aspart in CSII, the extremely short half-life of these insulins quickly leads to insulin deficiency if the delivery system is interrupted. Essential to the safe use of infusion devices is thorough patient education, frequent SMBG and/or CGM, and a backup plan for injecting long- and/or rapid-acting insulins in the event of insulin infusion device failure. CGM sensor-augmented insulin infusion devices integrate the information from the CGM to inform insulin delivery (Fig. 404-1). Currently, sensor communicating functions can interrupt basal insulin delivery during hypoglycemia (threshold suspension) or when hypoglycemia is anticipated (predictive suspension), which may be particularly useful for addressing nocturnal hypoglycemia. Hybrid closed-loop systems have recently become available that combine patient-directed preprandial boluses with automated adjustment of between-meal and basal insulin delivery based on CGM. Clinical experience with closed-loop systems is rapidly increasing and expanding. Bihormonal infusion devices that deliver both insulin and glucagon are under development.

**Other Agents That Improve Glucose Control** The role of amylin, a 37-amino-acid peptide co-secreted with insulin from pancreatic beta cells, in normal glucose homeostasis is uncertain. However, based on the rationale that patients who are insulin deficient are also amylin deficient, an analogue of amylin (pramlintide) was created and found to reduce postprandial glycemic excursions in individuals with type 1 or type 2 DM taking insulin. Pramlintide injected just before a meal slows gastric emptying and suppresses glucagon but does not alter insulin levels. Pramlintide is approved for insulin-treated patients with type 1 or type 2 DM. Addition of pramlintide produces a modest reduction in the $HbA_{1c}$ and seems to dampen meal-related glucose excursions. In type 1 DM, pramlintide is started as a 15-μg SC injection before each meal and titrated up to a maximum of 30–60 μg as tolerated. In type 2 DM, pramlintide is started as a 60-μg SC injection before each meal and may be titrated up to a maximum of 120 μg. The major side effects are nausea and vomiting, and dose escalations should be slow to limit these side effects. Because pramlintide slows gastric emptying, it may influence absorption of other medications and should not be used in combination with other drugs that slow gastrointestinal (GI) motility. The short-acting insulin given before the meal should initially be reduced to avoid hypoglycemia and then titrated as the effects of the pramlintide become evident. Because pramlintide suppresses glucagon, it may worsen hypoglycemia recovery and should not be used in patients with hypoglycemia unawareness.

## TYPE 2 DIABETES MELLITUS

**General Aspects** The goals of glycemia-controlling therapy for type 2 DM are similar to those in type 1 DM. Whereas glycemic control tends to dominate the management of type 1 DM, the care of individuals with type 2 DM must also include attention to the treatment of conditions associated with type 2 DM (e.g., obesity, hypertension, dyslipidemia, CVD) and detection/management of DM-related complications **(Fig. 404-2; Chap. 405)**. Reduction in cardiovascular risk is of paramount importance because this is the leading cause of mortality in these individuals.

Type 2 DM management should begin with MNT (discussed above). An exercise regimen to increase insulin sensitivity and promote weight loss should also be instituted. Pharmacologic approaches to the management of type 2 DM include oral glucose-lowering agents, insulin, and other agents that improve glucose control; most physicians and patients prefer oral glucose-lowering agents as the initial choice. Any therapy that improves glycemic control reduces "glucose toxicity" to beta cells and may improve endogenous insulin secretion. However, type 2 DM is a progressive disorder and ultimately requires multiple therapeutic agents and often insulin in most patients.

**Glucose-Lowering Agents** Advances in the therapy of type 2 DM have generated oral glucose-lowering agents that target different pathophysiologic processes in type 2 DM. Based on their mechanisms of action, glucose-lowering agents are subdivided into agents that increase insulin secretion, reduce glucose production, increase insulin sensitivity, enhance GLP-1 action, or promote urinary excretion of glucose **(Table 404-5)**. Glucose-lowering agents other than insulin (with the exception of amylin analogue) are ineffective in type 1 DM and should not be used for glucose management of severely ill individuals with type 2 DM. Insulin is sometimes the initial glucose-lowering agent in type 2 DM.

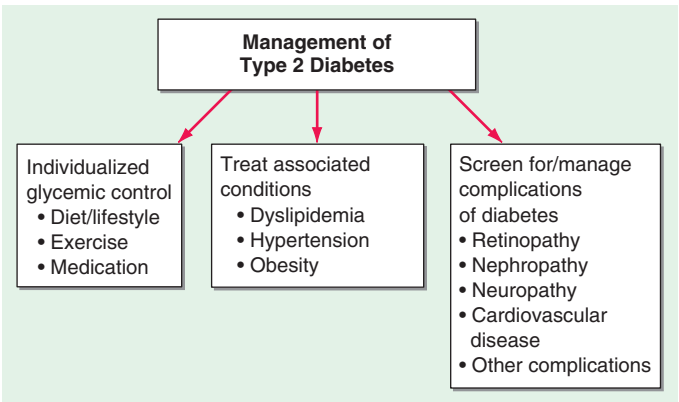


**FIGURE 404-2 Essential elements in comprehensive care of type 2 diabetes.**

**TABLE 404-5 Agents Used for Treatment of Type 1 or Type 2 Diabetes**

| | MECHANISM OF ACTION | EXAMPLES[a] | $HBA_{1C}$ REDUCTION (%)[b] | AGENT-SPECIFIC ADVANTAGES | AGENT-SPECIFIC DISADVANTAGES | CONTRAINDICATIONS |
|---|---|---|---|---|---|---|
| **Oral** | | | | | | |
| Biguanides[c**] | ↓ Hepatic glucose production, ↑ insulin sensitivity, influence gut function | Metformin | 1–2 | Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, ↓ CV events | Diarrhea, nausea, lactic acidosis, vitamin B12 deficiency | Renal insufficiency (see text for GFR <30 mL/min), CHF, radiographic contrast studies, hospitalized patients, acidosis |
| α-Glucosidase inhibitors[c***] | ↓ GI glucose absorption | Acarbose, miglitol, voglibose | 0.5–0.8 | Reduce postprandial glycemia | GI flatulence, elevated liver function tests | Renal/liver insufficiency |
| Dipeptidyl peptidase IV inhibitors[c***] | Prolong endogenous GLP-1 action; ↑ Insulin, ↓ glucagon | Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin | 0.5–0.8 | Well tolerated, do not cause hypoglycemia | Angioedema/urticarial and immune-mediated dermatologic effects | Reduced dose with renal insufficiency |
| Insulin secretagogues: Sulfonylureas[c*] | ↑ Insulin secretion | Glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glyburide, glyclopyramide | 1–2 | Short onset of action, lower postprandial glucose, inexpensive | Hypoglycemia, weight gain | Renal/liver insufficiency |
| Insulin secretagogues: Nonsulfonylureas[c***] | ↑ Insulin secretion | Mitiglinide, nateglinide, repaglinide | 0.5–1.0 | Short onset of action, lower postprandial glucose | Hypoglycemia | Renal/liver insufficiency (except repaglinide) |
| Sodium-glucose cotransporter 2 inhibitors[c***] | ↑ Renal glucose excretion | Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin | 0.5–1.0 | Do not cause hypoglycemia, ↓ weight and BP, renal protective, ↓ CV events | Urinary and genital infections, polyuria, dehydration, exacerbate tendency to hyperkalemia and DKA; see text | Moderate renal insufficiency, insulin-deficient DM[f] |
| Thiazolidinediones[c***] | ↓ Insulin resistance, ↑ glucose utilization | Pioglitazone, rosiglitazone | 0.5–1.4 | Lower insulin requirements | Peripheral edema, CHF, weight gain, fractures, macular edema | CHF, renal/liver insufficiency |
| **Parenteral/Oral** | | | | | | |
| GLP-1 receptor agonists[c***] | ↑ Insulin, ↓ glucagon, slow gastric emptying, satiety | Dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide (oral formulation available) | 0.5–1.0 | Weight loss, do not cause hypoglycemia (unless combined with another insulin secretagogue or insulin); ↓ CV events | Injection, nausea, pancreatitis[e] | Renal disease, agents that also slow GI motility; medullary carcinoma of thyroid, pancreatic disease |
| **Parenteral** | | | | | | |
| Amylin agonists[c,d***] | Slow gastric emptying, ↓ glucagon | Pramlintide | 0.25–0.5 | Reduce postprandial glycemia, weight loss | Injection, nausea, ↑ risk of hypoglycemia with insulin | Agents that also slow GI motility |
| Insulin[c,d****] | ↑ Glucose utilization, ↓ hepatic glucose production, and other anabolic actions | See text and Table 404-4 | Not limited | Known safety profile | Injection, weight gain, hypoglycemia | None |
| Medical nutrition therapy and physical activity[c*] | ↓ Insulin resistance, ↑ insulin secretion | Low-calorie, carbohydrate-controlled diet, exercise | 1–3 | Other health benefits | Compliance difficult, long-term success low | None |

[a]Examples are approved for use in the United States; others are available in other countries. Examples may not include all agents in the class. [b]$HbA_{1c}$ reduction (absolute) depends partly on starting $HbA_{1c}$. [c]Used for treatment of type 2 diabetes. [d]Used in conjunction with insulin for treatment of type 1 diabetes. Cost of agent in the United States: *low, **moderate, ***high, ****variable. [e]Degree of risk uncertain, avoid in individuals with risk factors for pancreatitis. [f]Risk of euglycemic DKA) in patients with insulin deficiency (e.g., type 1 diabetes).

*Note:* Some agents used to treat type 2 diabetes are not included in table (see text).

*Abbreviations:* CHF, congestive heart failure; CV, cardiovascular; GI, gastrointestinal; $HbA_{1c}$, glycosylated hemoglobin $A_{1c}$.

**BIGUANIDES** Metformin, representative of this class of agents, reduces hepatic glucose production and improves peripheral glucose utilization slightly (Table 404-5). Metformin activates AMP-dependent protein kinase and enters cells through organic cation transporters (polymorphisms of these may influence the response to metformin). Metformin acts in multiple tissues, but its mechanism of action remains undefined. There is evidence for reducing hepatic glucose production by antagonizing cAMP generation in hepatocytes as well as for actions in the gut. Metformin reduces fasting plasma glucose (FPG) and insulin levels, improves the lipid profile, and promotes modest weight loss. An extended-release form is available and may have fewer GI side effects (diarrhea, anorexia, nausea, metallic taste). Because of its metformin's relatively slow onset of action and GI symptoms with higher doses, the initial dose should be low and then escalated every 1–2 weeks to a maximally tolerated dose of 2000 mg daily. Metformin is effective as monotherapy and can be used in combination with other oral agents or with insulin. Long-term use is associated with reduced micro- and macrovascular complications. The major toxicity of metformin, lactic acidosis, is very rare and can be prevented by careful patient selection. Vitamin $B_{12}$ levels are lower during metformin treatment and should be monitored. Metformin should not be used in patients with moderate renal insufficiency (glomerular filtration rate [GFR] <30 mL/min), any

form of acidosis, unstable congestive heart failure (CHF), liver disease, or severe hypoxemia. Metformin should be discontinued in hospitalized patients, in patients who can take nothing orally, and in those receiving radiographic contrast material. Insulin should be used until metformin can be restarted.

**INSULIN SECRETAGOGUES—AGENTS THAT AFFECT THE ATP-SENSITIVE $K^+$ CHANNEL** Insulin secretagogues stimulate insulin secretion by interacting with the ATP-sensitive potassium channel on the beta cell **(Chap. 403)**. These drugs are most effective in individuals with type 2 DM of relatively recent onset (<5 years) who have residual endogenous insulin production. First-generation sulfonylureas (chlorpropamide, tolazamide, tolbutamide) have a longer half-life, a greater incidence of hypoglycemia, and more frequent drug interactions, and are no longer used. Second-generation sulfonylureas have a more rapid onset of action and better coverage of the postprandial glucose rise, but the shorter half-life of some agents may require more than once-a-day dosing. Sulfonylureas reduce both fasting and postprandial glucose and should be initiated at low doses and increased at 1- to 2-week intervals based on SMBG. In general, sulfonylureas increase insulin acutely and thus should be taken shortly before a meal; with chronic therapy, though, the insulin release is more sustained. Long-term use is associated with reduced micro- and macrovascular complications. Glimepiride and glipizide can be given in a single daily dose and are preferred over glyburide, especially in the elderly. Repaglinide, nateglinide, and mitiglinide are not sulfonylureas but also interact with the ATP-sensitive potassium channel. Because of their short half-life, these glinide agents are given immediately before each meal to reduce meal-related glucose excursions.

Insulin secretagogues, especially the longer acting ones, have the potential to cause hypoglycemia, especially in elderly individuals. Hypoglycemia is usually related to delayed meals, increased physical activity, alcohol intake, or renal insufficiency. Individuals who ingest an overdose of some agents develop prolonged and serious hypoglycemia and should be monitored closely in the hospital **(Chap. 406)**. Most sulfonylureas are metabolized in the liver to compounds (some of which are active, such as those of glyburide and the glinide nateglinide) that are cleared by the kidney. Thus, their use in individuals with significant hepatic or renal dysfunction is not advisable. For patients with chronic kidney disease requiring an insulin secretagogue, the shorter-acting sulfonylureas glimepiride or glipizide or the glinide repaglinide may be used with caution. Weight gain, a common side effect of sulfonylurea therapy, results from the increased insulin levels and improvement in glycemic control. Some sulfonylureas have significant drug interactions with alcohol and some medications including warfarin, aspirin, ketoconazole, α-glucosidase inhibitors, and fluconazole. A related isoform of ATP-sensitive potassium channels is present in the myocardium and the brain. All of these agents except glyburide have a low affinity for this isoform. Despite concerns that this agent might affect the myocardial response to ischemia and observational studies suggesting that sulfonylureas increase cardiovascular risk, studies have not shown an increased cardiac mortality with glyburide or other agents in this class.

**INSULIN SECRETAGOGUES—AGENTS THAT ENHANCE GLP-1 RECEPTOR SIGNALING** "Incretins" amplify glucose-stimulated insulin secretion **(Chap. 403)**. Agents that either act as a GLP-1 receptor agonist or enhance endogenous GLP-1 activity are approved for the treatment of type 2 DM (Table 404-5). Agents in this class do not cause hypoglycemia because of the glucose-dependent nature of incretin-stimulated insulin secretion (unless there is concomitant use of an agent that can lead to hypoglycemia—sulfonylureas, etc.). GLP-1 receptor agonists increase glucose-stimulated insulin secretion, suppress glucagon, and slow gastric emptying. These agents do not promote weight gain; in fact, most patients experience modest weight loss and appetite suppression. Short-acting GLP-1 receptor agonists are exenatide twice daily, liraglutide daily, and lixisenatide daily. Long-acting GLP-1 receptor agonists include sustained-release exenatide, dulaglutide, lixisenatide, and semaglutide, all administered weekly. Short-acting GLP-1 receptor agonists provide mostly postprandial coverage whereas the long-acting GLP-1 receptor agonists reduce both the postprandial and fasting glucose. Daily oral semaglutide is now available that depends on gastric absorption to avoid proteolytic degradation in the small intestine. All are modified to avoid enzymatic inactivation by dipeptidyl peptidase IV (DPP-IV) in the circulation.

For example, exenatide, a synthetic version of a peptide initially identified in the saliva of the Gila monster (exendin-4), is an analogue of GLP-1. Unlike native GLP-1, which has a half-life of ~2 min, differences in the exenatide amino acid sequence render it resistant to DPP-IV. Thus, exenatide has prolonged GLP-1-like action. Liraglutide, another GLP-1 receptor agonist, is almost identical to native GLP-1 except for an amino acid substitution and addition of a fatty acyl group (coupled with a γ-glutamic acid spacer) that promote binding to albumin and plasma proteins and prolong its half-life. Higher doses of liraglutide and semaglutide than used for glucose-lowering effects are effective for weight-loss therapy for obesity. Liraglutide treatment has also been associated with a decrease in CVD events in patients with type 2 DM and established CVD and with lower rates of diabetic kidney disease. In similar patient populations, semaglutide treatment has been associated with fewer CVD events and reduced diabetic kidney disease, but with an increased rate of retinopathy-related complications, while dulaglutide treatment has been associated with both a reduction in CVD events and in composite microvascular retinopathy and nephropathy-related complications primarily driven by prevention of renal events. Similar reductions in CVD events have not been observed with exenatide once weekly or lixisenatide. Treatment with GLP-1 receptor agonists should start at a low dose to minimize initial side effects (nausea being the limiting one). GLP-1 receptor agonists can be used as combination therapy with metformin, sulfonylureas, and thiazolidinediones. Some patients taking insulin secretagogues may require a reduction in those agents to prevent hypoglycemia. The major side effects are nausea, vomiting, and diarrhea. Some formulations carry a black box warning from the FDA because of an increased risk of thyroid C-cell tumors in rodents and are contraindicated in individuals with medullary carcinoma of the thyroid or multiple endocrine neoplasia. Because GLP-1 receptor agonists slow gastric emptying, they may influence the absorption of other drugs. Whether GLP-1 receptor agonists enhance beta cell survival or promote beta cell proliferation in humans as in rodents is not known, but these agents do not appear to alter the natural history of type 2 DM.

DPP-IV inhibitors inhibit degradation of native GLP-1 and thus enhance the incretin effect. DPP-IV, which is widely expressed on the cell surface of endothelial cells and some lymphocytes, degrades a wide range of peptides (not GLP-1 specific). DPP-IV inhibitors promote insulin secretion in the absence of hypoglycemia or weight gain and appear to have a preferential effect on postprandial blood glucose. The levels of GLP-1 action in the patient are greater with the GLP-1 receptor agonists than with DPP-IV inhibitors. DPP-IV inhibitors are used either alone or in combination with other oral agents in type 2 DM. Reduced doses should be given to patients with renal insufficiency. Allergy, including rash, hypersensitivity reactions (including anaphylaxis, angioedema, and Stevens-Johnson syndrome), and severe joint pain have been reported in association with DPP-IV inhibitors. There is evidence concerning a potentially increased risk for acute pancreatitis with GLP-1 receptor agonists and less so with DPP-IV inhibitors. For now, it is reasonable to avoid these agents in patients with pancreatic disease or with other significant risk factors for acute pancreatitis (e.g., heavy alcohol use, severely elevated serum triglycerides, hypercalcemia).

**α-GLUCOSIDASE INHIBITORS** α-Glucosidase inhibitors reduce postprandial hyperglycemia by delaying glucose absorption; they do not affect glucose utilization or insulin secretion (Table 404-5). Postprandial hyperglycemia, secondary to impaired hepatic and peripheral glucose disposal, contributes significantly to the hyperglycemic state in type 2 DM. These drugs, taken just before each meal, reduce glucose absorption by inhibiting the enzyme that cleaves oligosaccharides into simple sugars in the intestinal lumen. Therapy should be initiated at a

low dose with the evening meal and increased to a maximal dose over weeks to months. The major side effects (diarrhea, flatulence, abdominal distention) are related to increased delivery of oligosaccharides to the large bowel and can be reduced somewhat by gradual upward dose titration. α-Glucosidase inhibitors may increase levels of sulfonylureas and increase the incidence of hypoglycemia. Simultaneous treatment with bile acid resins and antacids should be avoided. These agents should not be used in individuals with inflammatory bowel disease, gastroparesis, or a serum creatinine >177 μmol/L (2 mg/dL). This class of agents is not as potent as other oral agents in lowering the $HbA_{1c}$ but is unique because it reduces the postprandial glucose rise. If hypoglycemia from other diabetes treatments occurs while taking these agents, the patient should consume glucose because the degradation and absorption of complex carbohydrates will be retarded.

**THIAZOLIDINEDIONES** Thiazolidinediones (Table 404-5) reduce insulin resistance by binding to the peroxisome proliferator-activated receptor γ (PPAR-γ) nuclear receptor (which forms a heterodimer with the retinoid X receptor). The PPAR-γ receptor is found at highest levels in adipocytes but is expressed at lower levels in many other tissues. Agonists of this receptor regulate a large number of genes, promote adipocyte differentiation, reduce hepatic fat accumulation, and promote fatty acid storage. Thiazolidinediones promote a redistribution of fat from central to peripheral locations. Circulating insulin levels decrease with use of the thiazolidinediones, indicating a reduction in insulin resistance. Although direct comparisons are not available, the two currently available thiazolidinediones appear to have similar efficacy. The prototype of this class of drugs, troglitazone, was withdrawn from the U.S. market after reports of hepatotoxicity and an association with an idiosyncratic liver reaction that sometimes led to hepatic failure. Although rosiglitazone and pioglitazone do not appear to induce the liver abnormalities seen with troglitazone, the FDA recommends measurement of liver function tests prior to initiating therapy. Modestly increased transaminase levels related to underlying fatty liver disease should not preclude treatment as these levels may improve with thiazolidinediones due to a reduction in hepatic fat content.

Rosiglitazone raises low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides slightly. Pioglitazone raises HDL to a greater degree and LDL a lesser degree but lowers triglycerides. The clinical significance of the lipid changes with these agents is not known and may be difficult to ascertain because most patients with type 2 DM are also treated with a statin.

Thiazolidinediones are associated with weight gain (2–3 kg), a small reduction in the hematocrit, and a mild increase in plasma volume. Peripheral edema and CHF are more common in individuals treated with these agents. These agents are contraindicated in patients with hepatic insufficiency or CHF (class III or IV). The FDA has issued an alert that rare patients taking these agents may experience a worsening of diabetic macular edema. An increased risk of fractures has been noted in postmenopausal women taking these agents. Thiazolidinediones have been shown to induce ovulation in premenopausal women with polycystic ovary syndrome. Women should be warned about the risk of pregnancy because the safety of thiazolidinediones in pregnancy is not established.

Concerns about increased cardiovascular risk associated with rosiglitazone led to considerable restrictions on its use and to the FDA issuing a black box warning in 2007. However, based on new information, the FDA has revised its guidelines and categorizes rosiglitazone similar to other drugs for type 2 DM. According to an FDA review, pioglitazone may be associated with an increased risk of bladder cancer. In one study, pioglitazone lowered the risk for recurrent stroke or myocardial infarction in insulin-resistant individuals without diabetes who had a prior stroke or transient ischemic attack.

**Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors** These agents (Table 404-5) lower the blood glucose by selectively inhibiting this co-transporter, which is expressed almost exclusively in the proximal, convoluted tubule in the kidney. This inhibits glucose reabsorption, lowers the renal threshold for glucose, and leads to increased urinary glucose excretion. Thus, the glucose-lowering effect is insulin independent and not related to changes in insulin sensitivity or secretion. The loss of urinary glucose may promote modest weight reduction. Since these agents also impair proximal reabsorption of sodium, their use is associated with a diuretic effect and 3–6 mmHg reduction in systolic blood pressure. Due to the increased urinary glucose, urinary and genital mycotic infections are more common in both men and women, and the diuretic effect can lead to reduced intravascular volume and acutely impaired kidney function. Inhibition of SGLT2 may lead to increased glucagon and consequently liver production of glucose and ketones. Euglycemic DKA may occur during illness or when ongoing glucosuria masks stress-induced requirements for insulin. These agents should not be prescribed for patients with type 1 DM or pancreatogenic forms of DM associated with insulin deficiency. Empagliflozin or canagliflozin reduces CVD events and all cause cardiovascular mortality in patients with type 2 DM and established CVD. All SGLT2 inhibitors may reduce hospitalization for CHF. Empagliflozin, canagliflozin, and dapagliflozin have all been shown to reduce progression of diabetic kidney disease but should not be initiated in patients with stage 3b CKD (eGFR <45 mL/min per 1.73 $m^2$) and should not be used with stage 4 CKD (eGFR <30 mL/min per 1.73 $m^2$). A possible increased risk of bladder cancer has been seen with dapagliflozin.

**OTHER THERAPIES FOR TYPE 2 DM • Bile Acid–Binding Resins** Evidence indicates that bile acids, by signaling through nuclear receptors, may have a role in metabolism. Bile acid metabolism is abnormal in type 2 DM. The bile acid–binding resin colesevelam has been approved for the treatment of type 2 DM (already approved for treatment of hypercholesterolemia). Because bile acid–binding resins are minimally absorbed into the systemic circulation, how bile acid–binding resins lower blood glucose is not known. The most common side effects are GI (constipation, abdominal pain, and nausea). Bile acid–binding resins can increase plasma triglycerides and should be used cautiously in patients with a tendency for hypertriglyceridemia. The role of this class of drugs in the treatment of type 2 DM is not yet defined.

**Bromocriptine** A formulation of the dopamine receptor agonist bromocriptine (Cycloset) has been approved by the FDA for the treatment of type 2 DM. However, its role in the treatment of type 2 DM is uncertain.

**INSULIN THERAPY IN TYPE 2 DM** Insulin should be considered as part of the initial therapy in type 2 DM, particularly in lean individuals or those with severe weight loss, in individuals with underlying renal or hepatic disease that precludes oral glucose-lowering agents, or in individuals who are hospitalized or acutely ill. Insulin therapy is ultimately required by a substantial number of individuals with type 2 DM because of the progressive nature of the disorder and the relative insulin deficiency that develops in patients with long-standing diabetes. Both physician and patient reluctance often delay the initiation of insulin therapy, but glucose control and patient well-being are improved by insulin therapy in patients who have not reached glycemic targets.

Because endogenous insulin secretion continues and is capable of providing some coverage of mealtime caloric intake, insulin is usually initiated in a single dose of long-acting insulin (0.1–0.4 U/kg per day), given in the evening or just before bedtime (NPH, glargine, detemir, or degludec). Because fasting hyperglycemia and increased hepatic glucose production are prominent features of type 2 DM, bedtime insulin is more effective in clinical trials than a single dose of morning insulin. Glargine given at bedtime has less nocturnal hypoglycemia than NPH insulin. Some physicians prefer a relatively low, fixed starting dose of long-acting insulin (5–15 units) or a weight-based dose (0.1 units/kg). The insulin dose may then be adjusted in 10–20% increments as dictated by SMBG results. Both morning and bedtime long-acting insulin may be used in combination with oral glucose-lowering agents. Initially, basal insulin may be sufficient, but often prandial insulin coverage with multiple insulin injections is needed as diabetes progresses (see insulin regimens used for type 1 DM). Other insulin formulations that have a combination of short-acting and long-acting

insulin (Table 404-4) are sometimes used in patients with type 2 DM because of convenience but do not allow independent adjustment of short-acting and long-acting insulin dose and often do not achieve the same degree of glycemic control as basal/bolus regimens. In selected patients with insulin-deficient type 2 DM, insulin infusion devices may be considered.

**CHOICE OF INITIAL GLUCOSE-LOWERING AGENT** The level of hyperglycemia and the patient's individualized goal (see "Establishment of Target Level of Glycemic Control") should influence the initial choice of therapy. Patients with mild hyperglycemia (FPG <7.0–11.0 mmol/L [126–199 mg/dL]) often respond well to a single, oral glucose-lowering agent, while those with moderate hyperglycemia (FPG 11.1–13.9 mmol/L [200–250 mg/dL]) will usually require more than one oral agent or insulin. Patients with more severe hyperglycemia (FPG >13.9 mmol/L [250 mg/dL]) may respond partially but are unlikely to achieve normoglycemia with oral therapy. Insulin can be used as initial therapy in individuals with severe hyperglycemia (FPG <13.9–16.7 mmol/L [250–300 mg/dL]) or in those who are symptomatic from the hyperglycemia. This approach is based on the rationale that more rapid glycemic control will reduce "glucose toxicity" to the islet cells, improve endogenous insulin secretion, and possibly allow oral glucose-lowering agents to be more effective. If this occurs, the insulin may be discontinued.

Insulin secretagogues, biguanides, α-glucosidase inhibitors, thiazolidinediones, GLP-1 receptor agonists, DPP-IV inhibitors, SLGT2 inhibitors, and insulin are approved for monotherapy of type 2 DM. Although each class of oral glucose-lowering agents has advantages and disadvantages (Table 404-5), certain generalizations apply: (1) insulin secretagogues, biguanides, GLP-1 receptor agonists, and thiazolidinediones improve glycemic control to a similar degree (1–2% reduction in $HbA_{1c}$) and are more effective than α-glucosidase inhibitors, DPP-IV inhibitors, and SLGT2 inhibitors; (2) insulin secretagogues, GLP-1 receptor agonists, DPP-IV inhibitors, α-glucosidase inhibitors, and SLGT2 inhibitors begin to lower the plasma glucose immediately, whereas the glucose-lowering effects of the biguanides and thiazolidinediones are delayed by weeks; (3) not all agents are effective in all individuals with type 2 DM; (4) biguanides, α-glucosidase inhibitors, GLP-1 receptor agonists, DPP-IV inhibitors, thiazolidinediones, and SLGT2 inhibitors do not directly cause hypoglycemia; (5) most individuals will eventually require treatment with more than one class of oral glucose-lowering agents or insulin, reflecting the progressive nature of type 2 DM; and (6) durability of glycemic control is slightly less for sulfonylureas compared to metformin or thiazolidinediones.

Considerable clinical experience exists with metformin and sulfonylureas because they have been available for several decades. It is assumed that the α-glucosidase inhibitors, GLP-1 receptor agonists, DPP-IV inhibitors, thiazolidinediones, and SLGT2 inhibitors will reduce DM-related complications by improving glycemic control. Pioglitazone may reduce CVD events through targeting a fundamental abnormality in type 2 DM, namely insulin resistance. A reduction in CVD events and in progression of diabetic kidney disease seen with some GLP-1 agonists and SGLT2 inhibitors may also operate through glucose-independent mechanisms **(Chap. 405)**.

Treatment algorithms by several professional societies (ADA/European Association for the Study of Diabetes [EASD], IDF, AACE) suggest metformin as initial therapy because of its efficacy, known side-effect profile, and low cost **(Fig. 404-3)**. Initiation of pharmacologic therapy should be accompanied by an emphasis on lifestyle modification (e.g., MNT, increased physical activity, and weight loss). Metformin's advantages are that it promotes mild weight loss, lowers insulin levels, and improves the lipid profile slightly. Based on SMBG results and the $HbA_{1c}$, the dose of metformin should be increased until the glycemic target is achieved or maximum dose is reached.

**COMBINATION THERAPY WITH GLUCOSE-LOWERING AGENTS** A number of combinations of therapeutic agents are successful in type 2 DM: metformin + second oral agent, metformin + GLP-1 receptor agonist, metformin + insulin, or combinations of a long-acting insulin and a GLP-1 receptor agonist. Because mechanisms of action of the first and second agents should be different, the effect on glycemic control is usually additive. There are little data to support the choice of one combination over another combination. Recent results from the NIH-funded Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE) indicated that addition of liraglutide or basal insulin to metformin leads to better glycemic control than glimepiride or sitagliptin (SLGT2 inhibitors were not studied). Based on recent demonstrations of a beneficial cardiovascular effect in certain individuals with type 2 DM and CVD, or at high risk of CVD, a GLP-1 receptor agonist or a SGLT2 inhibitor should now be considered in these populations. Medication costs vary considerably (Table 404-5), and this often factors into medication choice. Several fixed-dose combinations of oral agents are available, but evidence that they are superior to titration of a single agent to a maximum dose and then addition of a second agent is lacking. If adequate control is not achieved with the combination of two agents (based on reassessment of the $HbA_{1c}$ every 3 months), a third oral agent, GLP-1 receptor agonist, or basal insulin should be added (Fig. 404-3). Treatment approaches vary considerably from country to country. For example, α-glucosidase inhibitors are used commonly in South Asian patients (Indian), but infrequently in the United States or Europe. Whether this reflects an underlying difference in the disease or physician preference is not clear.

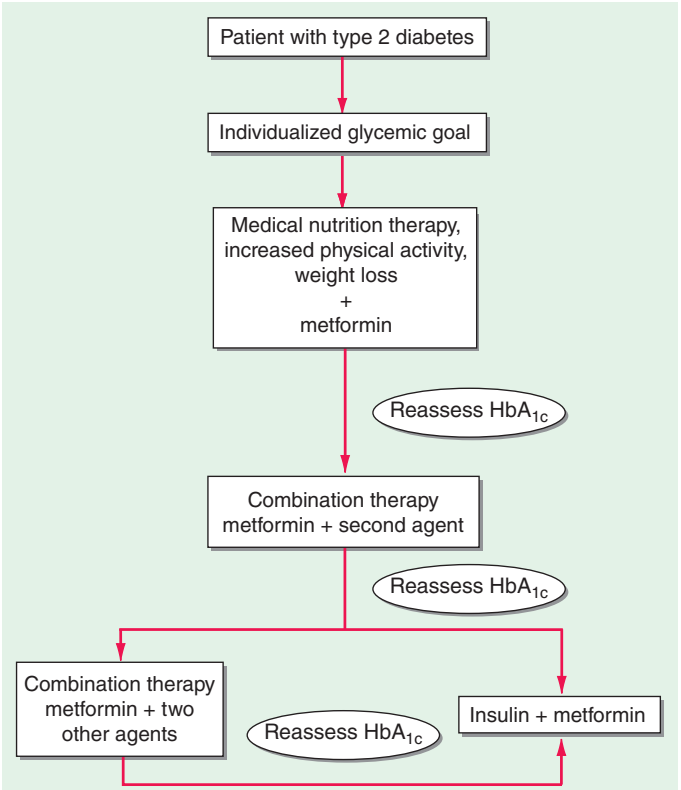


**FIGURE 404-3 Glycemic management of type 2 diabetes.** See text for discussion of treatment of severe hyperglycemia or symptomatic hyperglycemia. Agents that can be combined with metformin include insulin secretagogues, thiazolidinediones, α-glucosidase inhibitors, DPP-IV inhibitors, GLP-1 receptor agonists, SLGT2 inhibitors, and insulin. $HbA_{1c}$, hemoglobin $HbA_{1c}$.

Treatment with insulin often becomes necessary as type 2 DM enters the phase of relative insulin deficiency and is signaled by inadequate glycemic control with one or two oral glucose-lowering agents. Insulin alone or in combination should be used in patients who fail to reach glycemic targets. For example, a single dose of long-acting insulin at bedtime is often effective in combination with metformin. As endogenous insulin production falls further, multiple injections of long-acting together with short-acting insulin are necessary to control postprandial glucose excursions. These insulin regimens are identical to the long-acting and short-acting combination regimens discussed above for type 1 DM, although usually at higher doses given insulin resistance. Weight gain and hypoglycemia are the major adverse effects

of insulin therapy. The daily insulin dose required can become quite large (1–2 units/kg per day) as endogenous insulin production falls and insulin resistance persists. Individuals who require >1 unit/kg per day of long-acting insulin should be considered for combination therapy with metformin a GLP-1 receptor agonist, or a thiazolidinedione as these can reduce insulin requirements in some individuals with type 2 DM. Insulin plus a thiazolidinedione promotes weight gain and may be associated with peripheral edema. Addition of a thiazolidinedione to a patient's insulin regimen may necessitate a reduction in the insulin dose to avoid hypoglycemia. Patients requiring large doses of insulin (>200 units/day) can be treated with a more concentrated form of insulin.



### OTHER THERAPIES FOR DIABETES

Metabolic (also referred to as bariatric) surgery for obese individuals with type 2 DM has shown considerable promise, sometimes with dramatic resolution of the diabetes or major reductions in the needed dose of glucose-lowering therapies **(Chap. 402)**. Several large, nonrandomized clinical trials have demonstrated a much greater efficacy of metabolic surgery compared to medical management in the treatment of type 2 DM and may be considered in individuals with type 2 DM and a BMI >35 kg/m$^2$. The ADA clinical guidelines state that metabolic surgery should be considered in individuals with type 2 DM and a body mass index >30 kg/m$^2$ if hyperglycemia is inadequately controlled despite optimal medical therapy.

Short-term intense caloric restriction (very-low-calorie diet, typically 800–1000 calories/day) can dramatically improve type 2 DM, sometimes leading to resolution of the diabetes. Such an approach is more effective in recent-onset type 2 DM and should be supervised by a provider with expertise and should be followed by a long-term, weight-maintenance program.

Whole-pancreas transplantation can normalize glucose control in type 1 DM and when performed simultaneously with or after kidney transplantation can prolong the life of the kidney transplant by offering protection against recurrent diabetic nephropathy. Pancreatic islet transplantation is available as a less invasive form of beta-cell replacement therapy for type 1 DM, but it remains investigational in the United States. Due to the risks associated with chronic immunosuppression, whole-pancreas and pancreatic islet transplantation may be considered for patients with severe metabolic instability or already requiring immunosuppression in support of a kidney or other organ transplant. Patients with chronic pancreatitis and preserved islet function who require pancreatectomy for pain relief may benefit from autologous islet transplantation as this may prevent or ameliorate postsurgical DM.

### EMERGING THERAPIES

Many individuals with long-standing type 1 DM still produce very small amounts of insulin or have insulin-positive cells within the pancreas. This suggests that beta cells may slowly regenerate but are quickly destroyed by the autoimmune process. Particularly early in the disease course, efforts to suppress the autoimmune process, for example with anti-CD3 monoclonal antibodies that target T lymphocytes, are being tested at the time of diagnosis of type 1 DM, and for prevention in autoantibody-positive individuals at stages 1 and 2 of type 1 DM **(Chap. 403)**. Agents that target thioredoxin-interacting protein (TXNIP), especially Ca++ channel blockers, have some promise in recent-onset T1D and in rodent models of diabetes. Closed-loop insulin infusion devices that automate insulin delivery in response to changing glucose levels are progressing rapidly. New therapies under evaluation or development for type 2 DM include activators of glucokinase, inhibitors of 11 β-hydroxysteroid dehydrogenase-1, GPR40 agonists, dual agonists targeting the glucose-dependent insulinotropic polypeptide receptor and the GLP1-receptor, combined SLGT1 and SLGT2 inhibitors, and agents that may reduce inflammation, for example by inhibiting IL-1β.

Because whole-pancreas and pancreatic islet transplantation are both limited by organ availability from deceased donors, stem cell–derived islet cells and xenogeneic sources of islets may eventually allow for a limitless supply of insulin-producing cells for transplantation.

## ADVERSE EFFECTS OF THERAPY FOR DM

As with any therapy, the benefits of efforts directed toward glycemic control must be balanced against the risks of treatment (Table 404-5). Side effects of intensive treatment include an increased frequency of serious hypoglycemia, weight gain, increased economic costs, and greater demands on the patient. In the DCCT, quality of life was very similar in the intensive and standard therapy groups. The most serious complication of therapy for DM is hypoglycemia, and its treatment with oral glucose or glucagon injection is discussed in **Chap. 406**. Severe, recurrent, or unexplained hypoglycemia warrants examination of treatment regimen and glycemic goal for the individual patient. Weight gain occurs with most (insulin, insulin secretagogues, thiazolidinediones) but not all (metformin, α-glucosidase inhibitors, GLP-1 receptor agonists, DPP-IV inhibitors) therapies. The weight gain is partially due to the anabolic effects of insulin and the reduction in glucosuria.

## ACUTE DISORDERS RELATED TO SEVERE HYPERGLYCEMIA

Individuals with type 1 or type 2 DM and severe hyperglycemia (>13.9 mmol/L [250 mg/dL]) should be assessed for clinical stability, including mentation and hydration. Depending on the patient and the rapidity and duration of the severe hyperglycemia, an individual may require more intense and rapid therapy to lower the blood glucose. However, many patients with poorly controlled diabetes and hyperglycemia have few symptoms. The physician should assess if the patient is stable or if DKA or a hyperglycemic hyperosmolar state (HHS) should be considered. Ketones, an indicator of DKA, should be measured in individuals with type 1 DM when the plasma glucose is persistently >13.9 mmol/L (250 mg/dL), during a concurrent illness, or with symptoms such as nausea, vomiting, or abdominal pain. Blood measurement of β-hydroxybutyrate is preferred over urine testing with nitroprusside-based assays that measure only acetoacetate and acetone.

DKA and HHS are acute, severe disorders directly related to diabetes. DKA was formerly considered a hallmark of type 1 DM, but it also occurs in individuals with type 2 DM who can sometimes subsequently be treated with oral glucose-lowering agents (frequently in individuals of Hispanic or African-American descent). HHS is primarily seen in individuals with type 2 DM. Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and acid–base abnormalities. DKA and HHS exist along a continuum of hyperglycemia, with or without ketosis. The metabolic similarities and differences in DKA and HHS are highlighted in **Table 404-6**. Both disorders are associated with potentially serious complications if not promptly diagnosed and carefully treated.

### DIABETIC KETOACIDOSIS

**Clinical Features** The symptoms and physical signs of DKA are listed in **Table 404-7** and usually develop over 24 h. DKA may be the initial symptom complex that leads to a diagnosis of type 1 DM, but more frequently, it occurs in individuals with established diabetes. Nausea and vomiting are often prominent, and their presence in an individual with diabetes warrants laboratory evaluation for DKA. Abdominal pain may be severe and can resemble acute pancreatitis or ruptured viscus. Hyperglycemia leads to glucosuria, volume depletion, and tachycardia. Hypotension can occur because of volume depletion in combination with peripheral vasodilatation. Kussmaul respirations and a fruity odor on the patient's breath (secondary to metabolic acidosis and increased acetone) are classic signs of the disorder. Lethargy and central nervous system depression may evolve into coma with severe DKA but should also prompt evaluation for other reasons for altered mental status (e.g., infection, hypoxemia). Cerebral edema, an extremely serious complication of DKA, is seen most frequently in children. Signs of infection, which may precipitate DKA, should be sought on physical examination, even in the absence of fever. Failure to augment insulin therapy during physiologic stress often compounds the problem. Tissue ischemia (heart, brain) can also be a precipitating factor. Omission of insulin because of an infusion pump delivery site

**TABLE 404-6 Laboratory Values in Diabetic Ketoacidosis (DKA), Hyperglycemic Hyperosmolar State (HHS), and Euglycemic DKA (Representative Ranges at Presentation)**

| | DKA | HHS | EUGLYCEMIC DKA[c] |
|---|---|---|---|
| Glucose,[a] mmol/L (mg/dL) | 13.9–33.3 (250–600) | 33.3–66.6 (600–1200) | <11.1-13.9 (<200–250)[c] |
| Sodium, meq/L | 125–135 | 135–145 | ~135 |
| Potassium[a,b] | Normal to ↑ | Normal | Normal to ↑ |
| Magnesium[a] | Normal | Normal | Normal |
| Chloride[a] | Normal | Normal | Normal |
| Phosphate[a,b] | Normal | Normal | Normal |
| Creatinine | Slightly to moderately ↑ | Moderately ↑ | Slightly ↑ |
| Osmolality (mOsm/mL) | 300–320 | 330–380 | ~300 |
| Serum/urine ketones[a] | ++++ | +/– | ++++ |
| Serum β-hydroxybutyrate, mmol/L | >2.5 | <1.0 | >2.5 |
| Serum bicarbonate,[a] meq/L | <18 | >18 | <18 |
| Arterial pH | 6.8–7.3 | >7.3 | 6.8–7.3 |
| Arterial $PCO_2$,[a] mmHg | 20–30 | Normal | 20–30 |
| Anion gap[a] ($Na - [Cl + HCO_3]$) | ↑ | Normal to slightly ↑ | ↑ |

[a]Large changes occur during treatment of DKA. [b]Although plasma levels may be normal or high at presentation, total-body stores are usually depleted. [c]Sometimes occurs with SGLT2 inhibitor treatment; disproportionate glucosuria is consistent with SGLT2 inhibitor effect.

occlusion or device malfunction, eating disorder, mental health disorders, or an unstable psychosocial environment may sometimes be a factor precipitating DKA. Complete omission or inadequate administration of insulin by the patient or health care team (in a hospitalized patient with type 1 DM) may precipitate DKA.

**Pathophysiology** DKA results from relative or absolute insulin deficiency combined with counterregulatory hormone excess (glucagon, catecholamines, cortisol, and growth hormone). Both insulin deficiency and glucagon excess, in particular, are necessary for DKA to develop. The decreased ratio of insulin to glucagon promotes gluconeogenesis, glycogenolysis, and ketone body formation in the liver, as well as increases in substrate delivery from fat and muscle (free fatty acids, amino acids) to the liver. Ketosis results from a marked increase in free fatty acid release from adipocytes, with a resulting shift toward ketone body synthesis in the liver. Reduced insulin levels, in combination with elevations in catecholamines and growth hormone, also increase lipolysis and the release of free fatty acids. Markers of inflammation (cytokines, C-reactive protein) are elevated in both DKA and HHS.

**Laboratory Abnormalities and Diagnosis** The timely diagnosis of DKA is crucial and allows for prompt initiation of therapy. DKA is characterized by hyperglycemia (serum glucose >13.9 mmol/L [250 mg/dL], ketosis, and metabolic acidosis [serum bicarbonate <15–18 mmol/L with increased anion gap]) along with a number of secondary metabolic derangements (Table 404-6). Occasionally, the serum glucose is only minimally elevated and may even be normal (euglycemic DKA). This has been noted especially in individuals treated with SGLT2 inhibitors. Arterial pH usually ranges between 6.8 and 7.3, depending on the severity of the acidosis. Despite a total-body potassium deficit, the serum potassium at presentation may be mildly elevated, secondary to the acidosis and volume depletion. Total-body stores of sodium, chloride, phosphorus, and magnesium are also reduced in DKA but are not accurately reflected by their levels in the serum because of hypovolemia and hyperglycemia. Elevated blood urea nitrogen (BUN) and serum creatinine levels reflect intravascular volume depletion. Leukocytosis, hypertriglyceridemia, and hyperlipoproteinemia are commonly found as well. Hyperamylasemia may suggest a diagnosis of pancreatitis, especially when accompanied by abdominal pain. However, in DKA the amylase is usually of salivary origin and thus is not diagnostic of pancreatitis. Serum lipase should be obtained if pancreatitis is suspected.

The measured serum sodium is reduced as a consequence of the hyperglycemia (1.6-mmol/L [1.6-meq] reduction in serum sodium for each 5.6-mmol/L [100-mg/dL] rise in the serum glucose). A normal serum sodium in the setting of DKA indicates a more profound water deficit.

In DKA, the ketone body, β-hydroxybutyrate, is synthesized at a threefold greater rate than acetoacetate; however, acetoacetate is preferentially detected by a commonly used ketosis detection reagent (nitroprusside). Serum ketones are present at significant levels (usually positive at serum dilution of ≥1:8). The nitroprusside tablet, or stick, is often used to detect urine ketones; certain medications such as captopril or penicillamine may cause false-positive reactions. Serum or plasma assays for β-hydroxybutyrate are preferred because they more accurately reflect the true ketone body level.

The metabolic derangements of DKA exist along a spectrum, beginning with mild acidosis with moderate hyperglycemia evolving into more severe findings. The degree of acidosis and hyperglycemia do not necessarily correlate closely because a variety of factors determine the level of hyperglycemia (oral intake, urinary glucose loss). Ketonemia is a consistent finding in DKA and distinguishes it from simple hyperglycemia. The differential diagnosis of DKA includes starvation ketosis, alcoholic ketoacidosis (bicarbonate usually >15 meq/L), and other forms of increased anion-gap acidosis (Chap. 55).

**TABLE 404-7 Manifestations of Diabetic Ketoacidosis**

| Symptoms | Physical Findings |
|---|---|
| Nausea/vomiting | Tachycardia |
| Thirst/polyuria | Dehydration/hypotension |
| Abdominal pain | Tachypnea/Kussmaul respirations/ respiratory distress |
| Shortness of breath | Abdominal tenderness (may resemble acute pancreatitis or surgical abdomen) |
| **Precipitating events** | Lethargy/obtundation/cerebral edema/possibly coma |
| Inadequate insulin administration | |
| Infection (pneumonia/UTI/ gastroenteritis/sepsis) | |
| Infarction (cerebral, coronary, mesenteric, peripheral) | |
| Pancreatitis | |
| Drugs (cocaine) | |
| Pregnancy | |

*Abbreviation:* UTI, urinary tract infection.

## TREATMENT

### Diabetic Ketoacidosis

The management of DKA is outlined in Table 404-8. After initiating IV fluid replacement and insulin therapy, the agent or

**TABLE 404-8 Management of Diabetic Ketoacidosis**

1. Confirm diagnosis (↑ serum glucose, ↑ serum β-hydroxybutyrate, metabolic acidosis).
2. Admit to hospital; intensive care setting may be necessary for frequent monitoring, if pH <7.00, labored respiration, or impaired level of arousal.
3. Assess:
   Serum electrolytes ($K^+$, $Na^+$, $Mg^{2+}$, $Cl^-$, bicarbonate, phosphate)
   Acid-base status—pH, $HCO_3^-$, $PCO_2$, β-hydroxybutyrate
   Renal function (creatinine, urine output)
4. Replace fluids: 2–3 L of 0.9% saline or lactated Ringer's over first 1–3 h (10–20 mL/kg per hour); subsequently, 0.45% saline at 250–500 mL/h; change to 5% glucose and 0.45% saline or lactated Ringer's at 150–250 mL/h when blood glucose reaches 250 mg/dL (13.9 mmol/L).
5. Administer short-acting regular insulin: IV (0.1 units/kg), then 0.1 units/kg per hour by continuous IV infusion; increase two- to threefold if no response by 2–4 h. If the initial serum potassium is <3.3 mmol/L (3.3 meq/L), do not administer insulin until the potassium is corrected. Subcutaneous insulin may be used in uncomplicated, mild-moderate DKA with close monitoring.
6. Assess patient: What precipitated the episode (noncompliance, infection, trauma, pregnancy, infarction, cocaine)? Initiate appropriate workup for precipitating event (cultures, CXR, ECG, etc.).
7. Measure blood glucose every 1–2 h; measure electrolytes (especially $K^+$, bicarbonate, phosphate) and anion gap every 4 h for first 24 h.
8. Monitor blood pressure, pulse, respirations, mental status, fluid intake and output every 1–4 h.
9. Replace $K^+$: 10 meq/h when plasma $K^+$ <5.0–5.2 meq/L (or 20–30 meq/L of infusion fluid), ECG normal, urine flow and normal creatinine documented; administer 40–80 meq/h when plasma $K^+$ <3.5 meq/L or if bicarbonate is given. If initial serum potassium is >5.2 mmol/L (5.2 meq/L), do not supplement $K^+$ until the potassium is corrected.
10. See text about bicarbonate or phosphate supplementation.
11. Continue above until patient is stable, glucose goal is 8.3–11.1 mmol/L (150–200 mg/dL), and acidosis is resolved. Insulin infusion may be decreased to 0.02–0.1 units/kg per hour.
12. Administer long-acting insulin as soon as patient is eating. Allow for a 2- to 4-h overlap in insulin infusion and SC long-acting insulin injection.

*Abbreviations:* CXR, chest x-ray; ECG, electrocardiogram.

*Source:* Data from M Sperling, in *Therapy for Diabetes Mellitus and Related Disorders*, 3rd ed. Alexandria, VA: American Diabetes Association; 1998 and EA Nyenwe, AE Kitabchi: The evolution of diabetic ketoacidosis: An update of its etiology, pathogenesis and management. Metabolism 65:507, 2016.

event that precipitated the episode of DKA should be sought and aggressively treated. If the patient is vomiting or has altered mental status, a nasogastric tube should be inserted to prevent aspiration of gastric contents. Central to successful treatment of DKA is careful monitoring and frequent reassessment to ensure that the patient and the metabolic derangements are improving. A comprehensive flow sheet should record chronologic changes in vital signs, fluid intake and output, and laboratory values as a function of insulin administered.

After the initial bolus of normal saline or lactated Ringer's, replacement of the sodium and free water deficit is carried out over the next 24 h (fluid deficit is often 3–5 L). When hemodynamic stability and adequate urine output are achieved, IV fluids should be switched to 0.45% saline or lactated Ringer's depending on the calculated volume deficit. The change to 0.45% saline or using lactated Ringer's helps to reduce the trend toward hyperchloremia later in the course of DKA.

A bolus of IV (0.1 units/kg) short-acting regular insulin is usually administered immediately (Table 404-8), and subsequent treatment should provide continuous and adequate levels of circulating insulin. IV administration is usually preferred (0.1 units/kg of regular insulin per h) in patients with severe or complicated DKA because it ensures rapid distribution and allows adjustment of the infusion rate as the patient responds to therapy. Mild to moderate uncomplicated DKA can also be treated with SC short-acting insulin analogues. If chosen, IV regular insulin should be continued until the acidosis resolves and the patient is metabolically stable. As the acidosis and insulin resistance associated with DKA resolve, the insulin infusion rate can be decreased (to 0.02–0.1 units/kg per h). Long-acting insulin, in combination with SC short-acting insulin, should be administered as soon as the patient resumes eating, because this facilitates transition to an outpatient insulin regimen and reduces length of hospital stay. It is crucial to continue the insulin infusion or insulin SC until adequate insulin levels are achieved by administering long-acting insulin by the SC route. Even relatively brief periods of inadequate insulin administration in this transition phase may result in DKA relapse. In euglycemic DKA associated with SGLT2 inhibitors, the pharmacologic effect may persist for 10–14 days following discontinuation of SGLT2 inhibitor therapy as evidenced by ongoing glucosuria despite normoglycemia (glucose <180 mg/dL), during which time relapse of ketoacidosis is common if nutritional intake has not advanced (e.g., in the postoperative setting).

Hyperglycemia usually improves at a rate of 4.2–5.6 mmol/L (50–100 mg/dL) per h as a result of insulin-mediated glucose disposal, reduced hepatic glucose release, and rehydration. Rehydration reduces catecholamines, increases urinary glucose loss, and expands the intravascular volume. The decline in the plasma glucose within the first 1–2 h may be more rapid and is mostly related to volume expansion. When the plasma glucose reaches 11.1–13.9 mmol/L (200–250 mg/dL), glucose should be added to the 0.45% saline infusion to maintain the plasma glucose in the 8.3–11.1 mmol/L (150–200 mg/dL) range, and the insulin infusion should be continued at a lower rate to inhibit ketogenesis. More rapid correction of the serum glucose can precipitate the development of cerebral edema. Ketoacidosis begins to resolve as insulin reduces lipolysis, increases peripheral ketone body use, suppresses hepatic ketone body formation, and promotes bicarbonate regeneration. However, the acidosis and ketosis resolve more slowly than hyperglycemia. Depending on the rise of serum chloride, the anion gap (but not bicarbonate) will normalize. A hyperchloremic acidosis (serum bicarbonate of 15–18 mmol/L [15–18 meq/L]) often follows successful treatment and gradually resolves as the kidneys regenerate bicarbonate and excrete chloride.

Potassium stores are depleted in DKA (estimated deficit 3–5 mmol/kg [3–5 meq/kg]). During treatment with insulin and fluids, various factors contribute to the development of hypokalemia. These include insulin-mediated potassium transport into cells, resolution of the acidosis (which also promotes potassium entry into cells), and urinary loss of potassium salts of organic acids. Thus, potassium repletion should commence as soon as adequate urine output and a normal serum potassium are documented. If the initial serum potassium level is elevated, then potassium repletion should be delayed until the potassium falls into the normal range. Inclusion of 20–40 meq of potassium in each liter of IV fluid is reasonable, but additional potassium supplements may also be required. To reduce the amount of chloride administered, potassium phosphate or acetate can be substituted for the chloride salt. The goal is to maintain the serum potassium at >3.5 mmol/L (3.5 meq/L).

Despite a bicarbonate deficit, bicarbonate replacement is not usually necessary. In fact, theoretical arguments suggest that bicarbonate administration and rapid reversal of acidosis may impair cardiac function, reduce tissue oxygenation, and promote hypokalemia. The results of most clinical trials do not support the routine use of bicarbonate replacement, and one study in children found that bicarbonate use was associated with an increased risk of cerebral edema. However, in the presence of severe acidosis (arterial pH <7.0), sodium bicarbonate (50 mmol [meq/L] in 200 mL of sterile water with 10 meq/L KCl per h) may be administered for the first 2 h until the pH is >7.0. Hypophosphatemia may result from increased glucose usage, but randomized clinical trials have not demonstrated that phosphate replacement is beneficial in DKA. If the serum phosphate is <0.32 mmol/L (1 mg/dL), then phosphate supplement should be considered and the serum calcium monitored. Hypomagnesemia may develop during DKA therapy and may also require supplementation.

With appropriate therapy, the mortality rate of DKA is low (<1%) and is related more to the underlying or precipitating event, such as infection or myocardial infarction. Venous thrombosis, upper GI bleeding, and acute respiratory distress syndrome occasionally complicate DKA. The major nonmetabolic complication of DKA therapy is cerebral edema, which most often develops in children as DKA is resolving. The etiology of and optimal therapy for cerebral edema are not well established, but overreplacement of free water and rapid normalization of serum glucose should be avoided.

Following treatment, the physician and patient should review the sequence of events that led to DKA to prevent future recurrences. Foremost is patient education about the symptoms of DKA, its precipitating factors, and the management of diabetes during a concurrent illness.

### HYPERGLYCEMIC HYPEROSMOLAR STATE

**Clinical Features** The prototypical patient with HHS is an elderly individual with type 2 DM, with a several-week history of polyuria, weight loss, and diminished oral intake that culminates in mental confusion, lethargy, or coma. The physical examination reflects profound dehydration and hyperosmolality and reveals hypotension, tachycardia, and altered mental status. Notably absent are symptoms of nausea, vomiting, and abdominal pain and the Kussmaul respirations characteristic of DKA. HHS is often precipitated by a serious, concurrent illness such as myocardial infarction or stroke. Sepsis, pneumonia, and other serious infections are frequent precipitants and should be sought. In addition, a debilitating condition (prior stroke or dementia) or social situation that compromises water intake usually contributes to the development of the disorder.

**Pathophysiology** Relative insulin deficiency and inadequate fluid intake are the underlying causes of HHS. Insulin deficiency increases hepatic glucose production (through glycogenolysis and gluconeogenesis) and impairs glucose utilization in skeletal muscle (see above discussion of DKA). Hyperglycemia induces an osmotic diuresis that leads to intravascular volume depletion, which is exacerbated by inadequate fluid replacement. The absence of ketosis in HHS is not understood. Presumably, the insulin deficiency is only relative and less severe than in DKA. Lower levels of counterregulatory hormones and free fatty acids have been found in HHS than in DKA in some studies. It is also possible that the liver is less capable of ketone body synthesis or that the insulin/glucagon ratio does not favor ketogenesis.

**Laboratory Abnormalities and Diagnosis** The laboratory features in HHS are summarized in Table 404-6. Most notable are the marked hyperglycemia (plasma glucose may be >55.5 mmol/L [1000 mg/dL]), hyperosmolality (>350 mOsm/L), and prerenal azotemia. The measured serum sodium may be normal or slightly low despite the marked hyperglycemia. The corrected serum sodium is usually increased (add 1.6 meq to measured sodium for each 5.6-mmol/L [100-mg/dL] rise in the serum glucose). In contrast to DKA, acidosis and ketonemia are absent or mild. A small anion-gap metabolic acidosis may be present secondary to increased lactic acid. Moderate ketonuria, if present, is secondary to starvation.

## TREATMENT

### Hyperglycemic Hyperosmolar State

Volume depletion and hyperglycemia are prominent features of both HHS and DKA. Consequently, therapy of these disorders shares several elements (Table 404-8). In both disorders, careful monitoring of the patient's fluid status, laboratory values, and insulin infusion rate is crucial. Underlying or precipitating problems should be aggressively sought and treated. In HHS, fluid losses and dehydration are usually more pronounced than in DKA due to the longer duration of the illness. The patient with HHS is usually older, more likely to have mental status changes, and more likely to have a life-threatening precipitating event with accompanying comorbidities. Even with proper treatment, HHS has a substantially higher mortality rate than DKA (up to 15% in some clinical series).

Fluid replacement should initially stabilize the hemodynamic status of the patient (1–3 L of 0.9% normal saline over the first 2–3 h). Because the fluid deficit in HHS is accumulated over a period of days to weeks, the rapidity of reversal of the hyperosmolar state must balance the need for free water repletion with the risk that too rapid a reversal may worsen neurologic function. If the serum sodium is >150 mmol/L (150 meq/L), 0.45% saline should be used. After hemodynamic stability is achieved, the IV fluid administration is directed at reversing the free water deficit using hypotonic fluids (0.45% saline initially, then 5% dextrose in water [$D_5W$]). The calculated free water deficit (which can be as great as 9–10 L) should be reversed over the next 1–2 days (infusion rates of 200–300 mL/h of hypotonic solution). Potassium repletion is usually necessary and should be dictated by repeated measurements of the serum potassium. In patients taking diuretics, the potassium deficit can be quite large and may be accompanied by magnesium deficiency. Hypophosphatemia may occur during therapy and can be improved by using $KPO_4$ and beginning nutrition.

As in DKA, rehydration and volume expansion lower the plasma glucose initially, but insulin is also required. A reasonable regimen for HHS begins with an IV insulin bolus of 0.1 unit/kg followed by IV insulin at a constant infusion rate of 0.1 unit/kg per hour. If the serum glucose does not fall, increase the insulin infusion rate by twofold. As in DKA, glucose should be added to IV fluid when the plasma glucose falls to 11.1–13.9 mmol/L (200–250 mg/dL), and the insulin infusion rate should be decreased to 0.02–0.1 unit/kg per h. The insulin infusion should be continued until the patient has resumed eating and can be transferred to an SC insulin regimen. The patient should be discharged from the hospital on insulin, although some patients can later switch to oral glucose-lowering agents.

## MANAGEMENT OF DIABETES IN A HOSPITALIZED PATIENT

Virtually all medical and surgical subspecialties are involved in the care of hospitalized patients with diabetes. Hyperglycemia, whether in a patient with known diabetes or in someone without known diabetes, appears to be a predictor of poor outcome in hospitalized patients. General anesthesia, surgery, infection, or concurrent illness raises the levels of counterregulatory hormones (cortisol, growth hormone, catecholamines, and glucagon) and cytokines that may lead to transient insulin resistance and hyperglycemia. These factors increase insulin requirements by increasing glucose production and impairing glucose utilization and thus may worsen glycemic control. The concurrent illness or surgical procedure may lead to variable insulin absorption and also prevent the patient with DM from eating normally and, thus, may promote hypoglycemia. Glycemic control should be assessed on admission using the $HbA_{1c}$. Electrolytes, renal function, and intravascular volume status should be assessed as well. The high prevalence of CVD in individuals with DM (especially in type 2 DM) may necessitate preoperative cardiovascular evaluation (Chap. 405).

The goals of diabetes management during hospitalization are near-normoglycemia, avoidance of hypoglycemia, and transition back to the outpatient diabetes treatment regimen. Upon hospital admission, frequent glycemic monitoring should begin, as should planning for diabetes management after discharge. CGM in the hospital or ICU setting is not FDA-approved but is under study. Glycemic control appears to improve the clinical outcomes in a variety of settings, but optimal glycemic goals for the hospitalized patient are incompletely defined. In a number of cross-sectional studies of patients with diabetes, a greater degree of hyperglycemia was associated with worse cardiac, neurologic, and infectious outcomes. In some studies, patients who do not have preexisting diabetes but who develop modest blood glucose elevations during their hospitalization appear to benefit from achieving near-normoglycemia using insulin treatment. However, a large randomized clinical trial (Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation [NICE-SUGAR])

of individuals in the intensive care unit (ICU) (most of whom were receiving mechanical ventilation) found an increased mortality rate and a greater number of episodes of severe hypoglycemia with very strict glycemic control (target blood glucose of 4.5–6 mmol/L or 81–108 mg/dL) compared to individuals with a more moderate glycemic goal (target blood glucose of <10 mmol/L or 180 mg/dL). Currently, most data suggest that very strict blood glucose control in acutely ill patients likely worsens outcomes and increases the frequency of hypoglycemia. The ADA suggests the following glycemic goals for hospitalized patients: (1) in critically or non–critically ill patients: glucose of 7.8–10.0 mmol/L or 140–180 mg/dL; (2) in selected patients: glucose of 6.1–7.8 mmol/L or 110–140 mg/dL with avoidance of hypoglycemia; (3) the target range in the perioperative period should be 80–180 mg/dL (4.4–10.0 mmol/L).

Critical aspects for optimal diabetes care in the hospital include the following. (1) A hospital-wide system approach to treatment of hyperglycemia and prevention of hypoglycemia is needed. Inpatient diabetes management teams consisting of nurse practitioners and physicians are increasingly common. (2) Diabetes treatment plans should focus on the transition from the ICU and the transition from the inpatient to outpatient setting. (3) Adjustment of the discharge treatment regimen of patients whose diabetes was poorly controlled on admission (as reflected by the $HbA_{1c}$) is important.

The physician caring for an individual with diabetes in the perioperative period, during times of infection or serious physical illness, or simply when the patient is fasting for a diagnostic procedure must monitor the plasma glucose vigilantly, adjust the diabetes treatment regimen, and provide glucose infusion as needed. Hypoglycemia is frequent in hospitalized patients, and many of these episodes are avoidable. Hospital systems should have a diabetes management protocol to avoid inpatient hypoglycemia. Measures to reduce or prevent hypoglycemia include frequent glucose monitoring, but it is also important to prevent hypoglycemia by anticipating drops in insulin requirement by factors such as decreasing renal function, decreasing glucocorticoid doses, or interruption of nutrition (parenteral or enteral or PO).

Depending on the severity of the patient's illness and the hospital setting, the physician can use either an insulin infusion or SC insulin. Insulin infusions are preferred in the ICU or in a clinically unstable setting because the half-life of the infused insulin is quite short (minutes). The absorption of SC insulin may be variable in such situations. Insulin infusions can also effectively control plasma glucose in the perioperative period and when the patient is unable to take anything by mouth, although for relatively short (<4 h) procedures most patients can remain on SC insulin. Regular insulin is used rather than insulin analogues for IV insulin infusion because it is less expensive and equally effective. The physician must consider carefully the clinical setting in which an insulin infusion will be used, including whether adequate ancillary personnel are available to monitor the blood glucose frequently and whether they can adjust the insulin infusion rate to maintain the blood glucose within the optimal range. Insulin-infusion algorithms should integrate the insulin sensitivity of the patient, frequent blood glucose monitoring, and the trend of changes in the blood glucose to determine the insulin-infusion rate. Insulin-infusion algorithms jointly developed and implemented by nursing and physician staff are advised. Because of the short half-life of IV regular insulin, it is necessary to administer long-acting insulin prior to discontinuation of the insulin infusion (2–4 h before the infusion is stopped) to avoid a period of insulin deficiency.

In patients who are not critically ill or not in the ICU, basal or "scheduled" insulin is provided by SC, long-acting insulin supplemented by prandial and/or "corrective" insulin using a short-acting insulin (insulin analogues preferred). "Sliding scale," short-acting insulin alone, where no insulin is given unless the blood glucose is elevated, is inadequate for inpatient glucose management and should not be used. The short-acting, prandial insulin dose should include coverage for food consumption (based on anticipated carbohydrate intake) plus corrective insulin based on the patient's insulin sensitivity and the blood glucose. For example, if the patient is thin (and likely insulin-sensitive), an insulin correction factor might be 1 unit for each 2.7 mmol/L (50 mg/dL) over the glucose target. If the patient is obese and insulin-resistant, then the insulin correction factor might be 2 units for each 2.7 mmol/L (50 mg/dL) over the glucose target. It is critical to individualize the regimen and adjust the basal or "scheduled" insulin dose frequently, based on the corrective insulin required. A consistent carbohydrate-controlled diabetes meal plan for hospitalized patients provides a predictable amount of carbohydrate for a particular meal each day (but not necessarily the same amount for breakfast, lunch, and supper) and avoids concentrated sweets. Individuals with type 1 DM who are undergoing general anesthesia and surgery or who are seriously ill should receive continuous insulin, either through an IV insulin infusion, their insulin infusion device, or by SC administration of a reduced dose of long-acting insulin. Short-acting insulin alone is insufficient. Prolongation of a surgical procedure or delay in the recovery room is not uncommon and may result in periods of insulin deficiency leading to DKA. Insulin infusion is the preferred method for managing patients with type 1 DM over a prolonged (several hours) perioperative period or when serious concurrent illness is present (0.5–1.0 units/h of regular insulin). If the diagnostic or surgical procedure is brief (<4 h), a reduced dose of SC insulin may suffice (20–50% basal reduction, with short-acting bolus insulin withheld or reduced). This approach prevents interruption of insulin infusion device therapy, or for MDI, facilitates the transition back to long-acting insulin after the procedure. The blood glucose should be monitored frequently during the illness or in the perioperative period.

Individuals with type 2 DM can be managed with either an insulin infusion or SC long-acting insulin (20–50% reduction depending on clinical setting) plus preprandial, short-acting insulin. Oral glucose-lowering agents should be discontinued upon admission (or up to a week prior to planned admission for SGLT2 inhibitors) and are not useful in regulating the plasma glucose in clinical situations where the insulin requirements and glucose intake are changing rapidly. Moreover, these oral agents may be dangerous if the patient is fasting (e.g., hypoglycemia with sulfonylureas, euglycemic DKA with SGLT2 inhibitors) or at risk for declining kidney function due to, for example, radiographic contrast media or unstable CHF (lactic acidosis with metformin). Once clinically stable, oral glucose-lowering agents may be resumed in anticipation of discharge.

## SPECIAL CONSIDERATIONS IN DM

### TOTAL PARENTERAL NUTRITION (TPN)/TOTAL ENTERAL NUTRITION (TEN)

(See also Chap. 335) TPN or TEN greatly increases insulin requirements. In addition, individuals not previously known to have DM may become hyperglycemic during TPN or TEN and require insulin treatment. For TPN, IV insulin infusion is the preferred treatment for hyperglycemia, and rapid titration to the required insulin dose is done most efficiently using a separate insulin infusion. After the total insulin dose has been determined, a proportion of this insulin may be added directly to the TPN solution to cover the nutritional requirements for insulin, and adjusted based on the need for modified dosing of short-acting insulin. In TEN, hyperglycemia may be limited by using high-protein formulations, but often requires insulin treatment. Short-acting insulins should be used to cover bolus or continuous enteral feeding to minimize the risk for hypoglycemia should the TEN be interrupted or held. Patients with insulin deficiency (type 1 DM and pancreatogenic DM) should also receive long-acting insulin (0.1–0.2 units/kg per day) to cover basal insulin requirements should the TPN or TEN be interrupted or cycled.

### GLUCOCORTICOIDS

Glucocorticoids increase insulin resistance, decrease glucose utilization, increase hepatic glucose production, and impair insulin secretion. These changes lead to a worsening of glycemic control in individuals with DM and may precipitate hyperglycemia in other individuals. If new-onset hyperglycemia remains during chronic treatment with supraphysiologic doses of glucocorticoid (>5 mg of prednisone or equivalent), the DM may be called "steroid-induced diabetes." The

effects of glucocorticoids on glucose homeostasis are dose-related, usually reversible, most pronounced in the postprandial period, and dependent on the timing and type of glucocorticoid. If the FPG is near the normal range, oral diabetes agents (e.g., sulfonylureas, metformin) may be sufficient to reduce hyperglycemia. If the FPG is >11.1 mmol/L (200 mg/dL), oral agents are usually not efficacious, and insulin therapy is required. Short-acting insulin may be sufficient alone or together with long-acting insulin in order to control postprandial glucose excursions.

## DIABETES MANAGEMENT IN OLDER ADULTS

Diabetes is very common in older adults, being present in ~25% of individuals over the age of 65 years. Increasingly, individuals with many years of type 1 DM are part of the patient population. As discussed above, individualized therapeutic goals and modalities in older adults should consider biologic age, other comorbidities and risk factors (hypertension, CV disease, etc.), neurocognitive and physical functional status, living arrangements, social support, and other medications. For example, the $HbA_{1c}$ goal for a highly functional 80-year-old should be different from that for an individual with diabetes in long-term care (skilled nursing facilities). In the former, the $HbA_{1c}$ goal (<7.0–7.5%) and selected therapies may be similar to younger individuals whereas in an individual with complex/poor health or cognitive impairment, an $HbA_{1c}$ goal of <8.0–8.5% would be reasonable. Critical to diabetes management in all older individuals is the avoidance of hypoglycemia, which can worsen underlying cognitive impairment or CV disease. For individuals using CGM, <1% of time should be spent with glucose <70 mg/dL and spending >50% of time in the target range of 70–180 mg/dL is acceptable. Thus, medications that can cause hypoglycemia (insulin secretagogues, insulin) should be used carefully. In choosing medications for diabetes, the adverse effects (Table 404-5) should be considered (especially heart failure, renal insufficiency, etc.). Hypertension and dyslipidemia should be treated in elderly individuals with diabetes because there is clear benefit of blood pressure control with the benefit for lipid-lowering medications being less clearly demonstrated.

## REPRODUCTIVE ISSUES

Reproductive capacity in either men or women with DM appears to be normal. Menstrual cycles may be associated with alterations in glycemic control in women with DM. Pregnancy is associated with marked insulin resistance; the increased insulin requirements often precipitate DM and lead to the diagnosis of gestational diabetes mellitus (GDM). Glucose, which at high levels is a teratogen to the developing fetus, readily crosses the placenta, but insulin does not. Thus, hyperglycemia from the maternal circulation may stimulate insulin secretion in the fetus. The anabolic and growth effects of insulin may result in macrosomia. GDM complicates ~7% (range 1–14%) of pregnancies. The incidence of GDM is greatly increased in certain ethnic groups, including blacks and Latinas, consistent with a similar increased risk of type 2 DM. Current recommendations advise screening for glucose intolerance between weeks 24 and 28 of pregnancy in women not known to have diabetes. Therapy for GDM is similar to that for individuals with pregnancy-associated diabetes and involves MNT and insulin, if hyperglycemia persists. Oral glucose-lowering agents are not approved for use during pregnancy, but studies using metformin or glyburide have shown efficacy and have not found toxicity. With current practices, the morbidity and mortality rates of the mother with GDM and the fetus are not different from those in the nondiabetic population. Individuals who develop GDM are at marked increased risk for developing type 2 DM in the future and should be screened periodically for DM (see screening recommendations in **Chap. 403**). Most individuals with GDM revert to normal glucose tolerance after delivery, but some will continue to have overt diabetes or impairment of glucose tolerance after delivery. In addition, children of women with GDM appear to be at risk for obesity and glucose intolerance and have an increased risk of diabetes beginning in the later stages of adolescence.

Pregnancy in individuals with known DM requires meticulous planning and adherence to strict treatment regimens. Intensive insulin therapy and near-normalization of the $HbA_{1c}$ (<6.5%) are essential for individuals with existing DM who are planning pregnancy. Consideration should be given to insulin infusion and CGM devices that may help to improve glycemic control prior to conception since the most crucial period of glycemic control is soon after fertilization. The risk of fetal malformations is increased 4–10 times in individuals with uncontrolled DM at the time of conception, and normal blood glucose during the preconception period and throughout the periods of organ development in the fetus should be the goal, with more frequent monitoring of $HbA_{1c}$ every 2 months throughout gestation. Maintenance of the $HbA_{1c}$ <6.0–6.5% reduces the incidence and severity of fetal macrosomia and neonatal hypoglycemia related to fetal hyperinsulinism driven by elevated maternal glucose.

## LIPODYSTROPHIC DM

Lipodystrophy, or the loss of SC fat tissue, may be generalized in certain genetic conditions such as leprechaunism, or acquired as part of an autoimmune disorder. Generalized lipodystrophy is associated with leptin deficiency and severe insulin resistance and is often accompanied by acanthosis nigricans, hepatic steatosis, and severe hypertriglyceridemia. Recombinant human leptin (metreleptin) may allow for the achievement of metabolic control in generalized lipodystrophy, but is associated with the development of neutralizing antibodies and is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Partial lipodystrophy may also be caused by certain genetic or acquired (e.g., treatment of HIV infection) conditions that produce a metabolic syndrome of insulin resistance, ectopic fat accumulation (hepatic steatosis), and glucose intolerance and dyslipidemia. Treatment of early childhood cancer with total-body irradiation may affect adipose tissue development and predisposes survivors to similar metabolic syndrome of adipose tissue dysfunction with potentially severe insulin resistance, hepatic steatosis, hypertriglyceridemia, and diabetes.

**HIV-Associated Lipodystrophy** Protease inhibitors and nucleoside reverse transcriptase inhibitors used in the treatment of HIV disease **(Chap. 202)** have been associated with a centripetal accumulation of fat (visceral and abdominal area), accumulation of fat in the dorsocervical region, loss of extremity fat, decreased insulin sensitivity (elevations of the fasting insulin level and reduced glucose tolerance on IV glucose tolerance testing), hepatic steatosis, and dyslipidemia. Although many aspects of the physical appearance of these individuals resemble Cushing's syndrome, increased cortisol levels do not account for this appearance. The possibility remains that this is related to HIV infection or highly active antiretroviral therapy by some undefined mechanism, because the syndrome can be observed in individuals not treated with protease inhibitors. Therapy for HIV-related lipodystrophy and associated metabolic dysfunction may include metformin, especially for abdominal fat accumulation, pioglitazone, especially for lipoatrophy and hepatic steatosis. Tesamorelin, a growth hormone–releasing hormone analog, is effective for reducing excess abdominal fat but requires monitoring of the serum insulin-like growth factor-1 (IGF-1) level, and may worsen glucose tolerance or exacerbate hyperglycemia in individuals with diabetes.

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# 405 Diabetes Mellitus: Complications

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Diabetes-related complications affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. For many years in the United States, diabetes has been the leading cause of new blindness in adults, renal failure, and nontraumatic lower extremity amputation and is a leading contributor to coronary heart disease (CHD). Diabetes-associated microvascular complications usually do not appear until the second decade of hyperglycemia. In contrast, diabetes-associated CHD risk, related in part to insulin resistance and its resultant dyslipidemeia, may develop before hyperglycemia is established. Because type 2 diabetes mellitus (DM) often has a long asymptomatic period of hyperglycemia before diagnosis, many individuals with type 2 DM have both glucose-related and insulin resistance–related complications at the time of diagnosis. Fortunately, many of the diabetes-related complications can be prevented or mitigated with aggressive glycemic, lipid, and blood pressure control, as well as efforts at early detection.

Diabetes-related complications can be divided into vascular and nonvascular complications and are similar for type 1 and type 2 DM (Table 405-1). The vascular complications of DM are further subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications (CHD, peripheral arterial disease [PAD], cerebrovascular disease). Microvascular complications are diabetes-specific, whereas macrovascular complications have additional pathophysiologic features that are shared with the general population. Nonvascular complications include infections, skin changes, hearing loss, and increased risk of dementia and impaired cognitive function.

**TABLE 405-1 Diabetes-Related Complications**

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|---|
| Microvascular |
| Eye disease |
| Retinopathy (nonproliferative/proliferative) |
| Macular edema |
| Neuropathy |
| Sensory and motor (mono- and polyneuropathy) |
| Autonomic |
| Nephropathy (albuminuria and declining renal function) |
| Macrovascular |
| Coronary heart disease |
| Peripheral arterial disease |
| Cerebrovascular disease |
| Other |
| Gastrointestinal (gastroparesis, diarrhea) |
| Genitourinary (uropathy/sexual dysfunction) |
| Dermatologic |
| Infectious |
| Cataracts |
| Glaucoma |
| Cheiroarthropathy[a] |
| Periodontal disease |
| Hearing loss |
| Other comorbid conditions associated with type 1 or type 2 diabetes (relationship to hyperglycemia is uncertain): depression, obstructive sleep apnea, fatty liver disease, hip fracture, osteoporosis, cognitive impairment or dementia, low testosterone in men. |

[a]Thickened skin and reduced joint mobility.

## GLYCEMIC CONTROL AND COMPLICATIONS

The microvascular complications of both type 1 and type 2 DM result from chronic hyperglycemia (Fig. 405-1). Evidence implicating a causative role for chronic hyperglycemia in the development of macrovascular complications is less conclusive as other factors such as dyslipidemia and hypertension also play important roles in macrovascular complications. CHD events and mortality rate are two to four times greater in patients with type 2 DM, correlate with fasting and

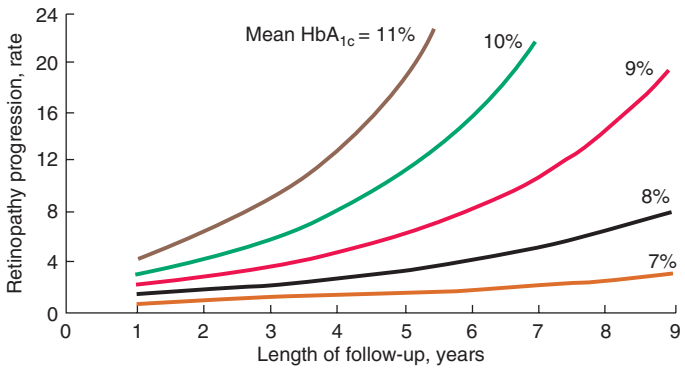


**FIGURE 405-1 Relationship of glycemic control and diabetes duration to diabetic retinopathy.** The progression of retinopathy in individuals in the Diabetes Control and Complications Trial is graphed as a function of the length of follow-up with different curves for different hemoglobin $A_{1c}$ ($HbA_{1c}$) values. *(Modified with permission from The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 44:968, 1995.)*

postprandial plasma glucose levels as well the hemoglobin $A_{1c}$ ($HbA_{1c}$), and can be reduced by intensive diabetes management as demonstrated in patients with type 1 DM.

The Diabetes Control and Complications Trial (DCCT) provided definitive proof that reduction in chronic hyperglycemia can prevent many complications of type 1 DM (Fig. 405-1). This large multicenter clinical trial randomized >1400 individuals with type 1 DM to either intensive or conventional diabetes management and prospectively evaluated the development of diabetes-related complications during a mean follow-up of 6.5 years. Individuals in the intensive diabetes management group received insulin by multiple daily injections or pump delivery along with extensive educational, psychological, and medical support, and achieved a substantially lower $HbA_{1c}$ (7.3%) than individuals in the conventional diabetes management group (9.1%). After the DCCT results were reported in 1993, study participants were all offered intensive therapy and continue to be followed in the Epidemiology of Diabetes Intervention and Complications (EDIC) trial, which has completed >30 years of follow-up (DCCT + EDIC). During the subsequent follow-up of >18 years, the initial separation in glycemic control disappeared with both arms maintaining a mean $HbA_{1c}$ of 8.0%, allowing assessment of a legacy effect of 6.5 years of near-normoglycemia on the development of long-term complications.

The DCCT phase demonstrated that improvement of glycemic control reduced nonproliferative and proliferative retinopathy (47% reduction), albuminuria (39% reduction), clinical nephropathy (54% reduction), and neuropathy (60% reduction). Improved glycemic control also slowed the progression of early diabetic complications. During the DCCT phase, weight gain (4.6 kg) and severe hypoglycemia (requiring assistance of another person to treat) were more common in the intensive therapy group. The benefits of an improvement in glycemic control occurred over the entire range of elevated $HbA_{1c}$ values (Fig. 405-1). The results of the DCCT predicted that individuals in the intensive diabetes management group would gain 7.7 additional years of vision, 5.8 additional years free from end-stage renal disease (ESRD), and 5.6 years free from lower extremity amputations. If all complications of DM were combined, individuals in the intensive diabetes management group would experience >15.3 more years of life without significant microvascular complications of DM, compared to individuals who received standard therapy. This translates into an additional 5.1 years of life expectancy for individuals in the intensive diabetes management group. The 30-year follow-up data in the intensively treated group show a continued reduction in retinopathy, nephropathy, and cardiovascular disease. For example, individuals in the intensive therapy group had a 42–57% reduction in cardiovascular events (nonfatal myocardial infarction [MI], stroke, or death from a cardiovascular event) at a mean follow-up of 18 years, even though their subsequent glycemic control was the same as those in the conventional diabetes management group from years 6.5 to 17. During the EDIC phase, <1% of the cohort had become blind, lost a limb to amputation, or required dialysis. Other complications of diabetes, including autonomic neuropathy, bladder and sexual dysfunction, and cardiac autonomic neuropathy, were reduced in the intensive therapy group.

The United Kingdom Prospective Diabetes Study (UKPDS) studied the course of >5000 individuals with type 2 DM for >10 years. This study used multiple treatment regimens and monitored the effect of intensive glycemic control and risk factor treatment on the development of diabetic complications. Newly diagnosed individuals with type 2 DM were randomized to (1) intensive management using various combinations of insulin, a sulfonylurea, or metformin or (2) conventional therapy using dietary modification and pharmacotherapy with the goal of symptom prevention. In addition, individuals were randomly assigned to different antihypertensive regimens. Individuals in the intensive treatment arm achieved an $HbA_{1c}$ of 7% compared to 7.9% in the standard treatment group. The UKPDS demonstrated that each percentage point reduction in $HbA_{1c}$ was associated with a 35% reduction in microvascular complications. As in the DCCT, there was a continuous relationship between glycemic control and development of complications. Improved glycemic control also reduced the cardiovascular event rate in the follow-up period of >10 years.

One of the major findings of the UKPDS was that strict blood pressure control significantly reduced both macro- and microvascular complications. In fact, the beneficial effects of blood pressure control were greater than the beneficial effects of glycemic control. Lowering blood pressure to moderate goals (144/82 mmHg) reduced the risk of DM-related death, stroke, microvascular endpoints, retinopathy, and heart failure (risk reductions between 32 and 56%). The American Diabetes Association (ADA) recommends blood pressure control <130/80 mmHg for individuals with high cardiovascular risk and <140/90 mmHg for individuals with lower cardiovascular risk.

Similar reductions in the risks of retinopathy and nephropathy were also seen in a small trial of lean Japanese individuals with type 2 DM randomized to either intensive glycemic control or standard therapy with insulin (Kumamoto study). These results demonstrate the effectiveness of improved glycemic control in individuals of different ethnicity and, presumably, a different etiology of DM (i.e., phenotypically different from those in the DCCT and UKPDS). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trials also found that improved glycemic control reduced microvascular complications.

Thus, these large clinical trials in type 1 and type 2 DM indicate that chronic hyperglycemia plays a causative role in the pathogenesis of diabetic micro- and macrovascular complications. In both the DCCT and the UKPDS, cardiovascular events were reduced at follow-up of >10 years, even though the improved glycemic control was not maintained. This legacy effect for a positive impact of a period of improved glycemic control on later diabetes complications has been attributed to the benefits of *metabolic memory*. Of note, despite long-standing DM, some individuals never develop retinopathy or nephropathy, suggesting a genetic susceptibility for developing particular complications.

## MECHANISMS OF COMPLICATIONS

Chronic hyperglycemia is the important etiologic factor leading to complications of DM, but the mechanism(s) by which it leads to such diverse cellular and organ dysfunction is unknown. The complications are likely multifactorial with an emerging hypothesis that hyperglycemia leads to epigenetic changes **(Chap. 466)** that influence gene expression in affected cells. Chronic hyperglycemia leads to formation of advanced glycosylation end products (AGEs; e.g., pentosidine, glucosepane, and carboxymethyllysine), which bind to specific cell surface receptor and/or the nonenzymatic glycosylation of intra- and extracellular proteins, leading to cross-linking of proteins, glomerular dysfunction, endothelial dysfunction, altered extracellular matrix composition, and accelerated atherosclerosis. The reduction of cellular glucose entry afforded in certain tissues such as myocardium and renal tubular epithelium through inhibition of the sodium glucose co-transporter-2 (SGLT-2) may contribute to the reduction in CHD events and renoprotective effects.

Growth factors may play an important role in some diabetes-related microvascular complications, and their production is increased by most of these proposed pathways. For example, vascular endothelial growth factor A (VEGF-A) is increased locally in diabetic proliferative retinopathy, decreases after laser photocoagulation, and is the target inhibited by intravitreous injection therapy. A possible unifying mechanism is that hyperglycemia leads to increased production of reactive oxygen species or superoxide in the mitochondria and this may activate several pathways. Although hyperglycemia serves as the initial trigger for complications of diabetes, it is still unknown whether the same pathophysiologic processes are operative in all complications or whether some pathways predominate in certain organs.

The mechanisms of diabetes-related macrovascular complications including MI and stroke are glucose-related mechanisms but also include traditional cardiovascular risk factors (dyslipidemia, hypertension) and insulin resistance. In type 2 diabetes, insulin resistance is present years prior to diagnosis and is associated with obesity and ectopic accumulation of lipids in muscle and liver. Additionally, insulin fails to appropriately suppress lipolysis from adipose tissue, which results in increased delivery of fatty acids to liver, muscle, endothelial cells, and

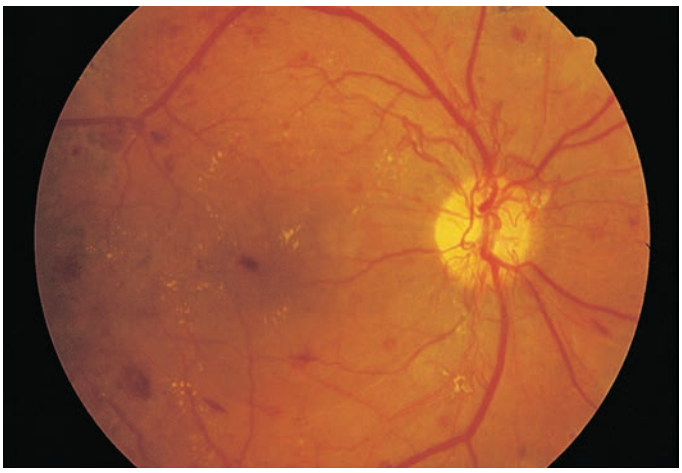

**FIGURE 405-2 Diabetic retinopathy results in scattered hemorrhages, yellow exudates, and neovascularization.** This patient has neovascular vessels proliferating from the optic disc, requiring urgent panretinal laser photocoagulation.

cardiac tissues, leading to tissue accumulation of triglycerides, diacylglycerol, and ceramides.

## OPHTHALMOLOGIC COMPLICATIONS OF DIABETES MELLITUS

DM is the leading cause of blindness between the ages of 20 and 74 in the United States. Severe vision loss is primarily the result of progressive diabetic retinopathy, which leads to significant macular edema and new blood vessel formation. Diabetic retinopathy is classified into two stages: nonproliferative and proliferative. Nonproliferative diabetic retinopathy usually appears late in the first decade or early in the second decade of hyperglycemia and is marked by retinal vascular microaneurysms, blot hemorrhages, and cotton-wool spots **(Fig. 405-2)**. Mild nonproliferative retinopathy may progress to more extensive disease, characterized by changes in venous vessel caliber, intraretinal microvascular abnormalities, and more numerous microaneurysms and hemorrhages. The pathophysiologic mechanisms invoked in nonproliferative retinopathy include loss of retinal pericytes, increased retinal vascular permeability, alterations in retinal blood flow, and abnormal retinal microvasculature, all of which can lead to retinal ischemia.

The appearance of neovascularization in response to retinal hypoxemia is the hallmark of proliferative diabetic retinopathy (Fig. 405-2). These newly formed vessels appear near the optic nerve and/or macula and rupture easily, leading to vitreous hemorrhage, fibrosis, and ultimately retinal detachment. Not all individuals with nonproliferative retinopathy go on to develop proliferative retinopathy, but the more severe the nonproliferative disease, the greater the chance of evolution to proliferative retinopathy within 5 years. This creates an important opportunity for early detection and treatment of diabetic retinopathy. Clinically significant macular edema can occur in the context of nonproliferative or proliferative retinopathy. Fluorescein angiography and optical coherence tomography are useful to detect macular edema, which is associated with a 25% chance of moderate visual loss over the next 3 years. Duration of DM and degree of glycemic control are the best predictors of the development of retinopathy; hypertension, nephropathy, and dyslipidemia are also risk factors. Nonproliferative retinopathy is found in many individuals who have had DM for >20 years. Although there is genetic susceptibility for retinopathy, it confers less influence than either the duration of DM or the degree of glycemic control.

# TREATMENT

## Diabetic Retinopathy

The most effective therapy for diabetic retinopathy is prevention. Intensive glycemic and blood pressure control will delay the development and slow the progression of retinopathy in individuals with either type 1 or type 2 DM. Paradoxically, during the first 6–12 months of improved glycemic control, established diabetic retinopathy may transiently worsen. Fortunately, this progression is temporary, and in the long term, improved glycemic control is associated with less diabetic retinopathy. Individuals with known retinopathy may be candidates for prophylactic laser photocoagulation when initiating intensive therapy, and especially prior to pancreas or islet transplantation that can rapidly normalize glycemia. Women with type 1 or type 2 DM who are planning pregnancy should be screened prior to and during pregnancy. Once advanced retinopathy is present, improved glycemic control imparts less benefit, although adequate ophthalmologic care can prevent most blindness. Lowering elevated levels of triglycerides with fenofibrate may reduce the progression of retinopathy.

Regular, comprehensive eye examinations are essential for all individuals with DM (see Table 404-1). Most diabetic eye disease can be successfully treated if detected early. Routine, nondilated eye examinations by the primary care provider or diabetes specialist are inadequate to detect diabetic eye disease, which requires a dilated eye exam performed by an optometrist or ophthalmologist, and subsequent management by a retinal specialist. Treatment of severe nonproliferative or proliferative retinopathy or macular edema with laser photocoagulation and/or anti-VEGF therapy (intravitreous injection) usually is successful in preserving vision. Aspirin therapy (up to 650 mg/d) does not appear to influence the natural history of diabetic retinopathy, and antiplatelet agents and anticoagulation may be continued in patients receiving intravitreal injections of anti-VEGF agents. Patients with severe proliferative retinopathy with vitreous hemorrhage and/or traction involving the macula often require surgical vitrectomy.

## RENAL COMPLICATIONS OF DIABETES MELLITUS

Diabetic nephropathy is the leading cause of chronic kidney disease (CKD) and ESRD requiring renal replacement therapy. CKD in individuals with DM is associated with an increased risk of cardiovascular disease, and the prognosis of individuals with diabetes on dialysis is poor. Individuals with diabetic nephropathy commonly have diabetic retinopathy. The presence of CKD in individuals with DM and no retinopathy should prompt investigation for alternative causes of kidney disease.

Like other microvascular complications, the pathogenesis of diabetic nephropathy is related to chronic hyperglycemia. The mechanisms by which chronic hyperglycemia leads to diabetic nephropathy, although incompletely defined, involve the effects of soluble factors (growth factors, angiotensin II, endothelin, AGEs), hemodynamic alterations in the renal microcirculation (glomerular hyperfiltration or hyperperfusion, increased glomerular capillary pressure), and structural changes in the glomerulus (increased extracellular matrix, basement membrane thickening, mesangial expansion, fibrosis). Some of these effects may be mediated through angiotensin II and mineralocorticoid receptors. Smoking accelerates the decline in renal function. Because only 20–40% of patients with diabetes develop diabetic nephropathy, additional genetic or environmental susceptibility factors likely contribute. Known risk factors include a family history of diabetic nephropathy. Diabetic nephropathy and ESRD secondary to DM develop more commonly in blacks, Native Americans, and Hispanic individuals with diabetes.

The natural history of diabetic nephropathy is characterized by a sequence of events that was initially defined for individuals with type 1 DM but appears similar in type 2 DM **(Fig. 405-3)**. Glomerular hyperperfusion and renal hypertrophy occur in the first years after the onset of DM and are associated with an increase of the estimated glomerular filtration rate (GFR). During the first 5 years of DM, thickening of the glomerular basement membrane, glomerular hypertrophy, and mesangial volume expansion occur as the GFR returns to normal. After 5–10 years of type 1 DM, many individuals begin to excrete small amounts of albumin in the urine. The ADA defines albuminuria as a persistently increased urinary albumin-to-creatinine ratio >30 mg/g

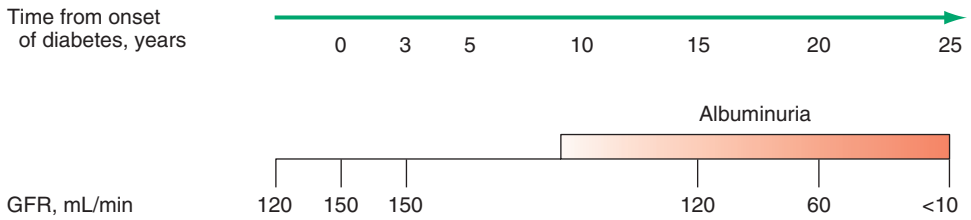


**FIGURE 405-3 Time course of development of diabetic nephropathy.** The relationship of time from onset of diabetes, albuminuria, and the glomerular filtration rate (GFR) are shown. This figure is typical for type 1 diabetes; individuals with type 2 diabetes may present with a lower GFR at the time of diagnosis.



on a spot specimen. In some individuals with DM and albuminuria of short duration, the albuminuria can regress with improvement in glycemic control **(Fig. 405-4)** or with improvement in blood pressure control using angiotensin-aldosterone system blockade and/or SGLT-2 inhibitor therapy. Diabetic kidney disease refers to albuminuria and reduced GFR (<60 mL/min per 1.73 $m^2$); CKD related to diabetes, which may not be accompanied by albuminuria, is also discussed in **Chap. 311**. Once there is marked albuminuria and a reduction in GFR, the pathologic changes are likely irreversible.

The nephropathy that develops in type 2 DM differs from that of type 1 DM in that albuminuria may be present when type 2 DM is diagnosed, reflecting its long asymptomatic period, and hypertension more often contributes to albuminuria and reduced GFR. Finally, it should be noted that albuminuria in type 2 DM may be secondary to factors unrelated to DM, such as hypertension, congestive heart failure (CHF), prostate disease, or infection.

As part of comprehensive diabetes care **(Chap. 404)**, albuminuria should be detected at an early stage when effective therapies can be instituted. Because some individuals with type 1 or type 2 DM have a decline in GFR in the absence of albuminuria, assessment should include a spot urinary albumin-to-creatinine ratio and an estimated GFR. The urine protein measurement by routine urinalysis does not detect low levels of albumin excretion. Screening for albuminuria should commence 5 years after the onset of type 1 DM and at the time of diagnosis of type 2 DM.

Type IV renal tubular acidosis (hyporeninemic hypoaldosteronism) may occur in type 1 or 2 DM. These individuals develop a propensity to hyperkalemia and acidemia, which may be exacerbated by medications (especially angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], and mineralocorticoid receptor antagonists). Patients with DM are predisposed to radiocontrast-induced nephrotoxicity. Risk factors for radiocontrast-induced nephrotoxicity are preexisting nephropathy and volume depletion. Individuals with DM undergoing radiographic procedures with contrast dye should be well hydrated before and after dye exposure, and the serum creatinine should be monitored for 24–48 h following the procedure. Metformin should be held until postintervention confirmation of preserved kidney function.

## TREATMENT

### Diabetic Nephropathy

The optimal therapy for diabetic nephropathy is prevention by control of glycemia (**Chap. 404 outlines glycemic goals and approaches**). Interventions effective in slowing progression of

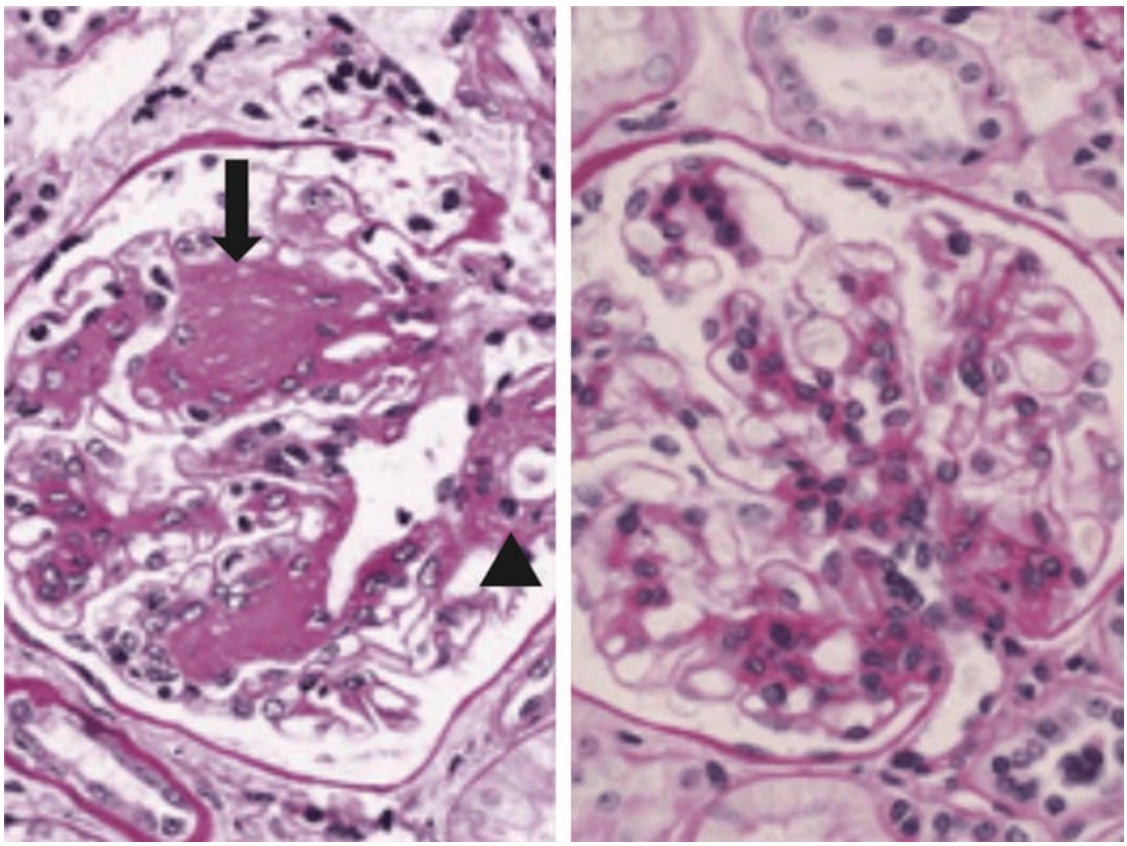

**FIGURE 405-4 Diabetic glomerular changes in a patient with type 1 diabetes** are reversed by 10 years of normoglycemia as a result of pancreas transplantation. Left panel shows diabetic glomerulosclerosis (*arrow*) and arteriolar hyalinosis (*arrowhead*) on kidney biopsy. Right panel shows a near-normal glomerulus in the same patient after 10 years of normoglycemia from pancreas transplantation. *(Reproduced with permission from P Fioretto et al: Reversal of lesions of diabetic nephropathy after pancreas transplantation. N Engl J Med 339:69, 1998.)*

albuminuria and declining kidney function include (1) improved glycemic control, (2) strict blood pressure control, (3) administration of an ACE inhibitor or ARB, and (4) in individuals with type 2 DM, administration of a SGLT-2 inhibitor. Dyslipidemia should also be treated.

Improved glycemic control reduces the rate at which albuminuria appears and progresses in type 1 and type 2 DM. However, once there is a large amount of albuminuria, it becomes more difficult for improved glycemic control to slow progression of renal disease, although 10-years of normoglycemia resulting from pancreas transplantation may lead to regression of mesangial glomerular lesions (Fig. 405-4). During the later phase of declining renal function, insulin requirements may fall as the kidney is a site of insulin degradation. As the GFR decreases with progressive nephropathy, the use and dose of glucose-lowering agents should be reevaluated (**see Table 404-5**). Some glucose-lowering medications (sulfonylureas and metformin) are contraindicated in advanced renal insufficiency, while others may require dose adjustment (glinides and DPP-4 inhibitors).

Many individuals with type 1 or type 2 DM develop hypertension. Numerous studies in both type 1 and type 2 DM demonstrate the effectiveness of strict blood pressure control in reducing albumin excretion and slowing the decline in renal function. Blood pressure should be maintained at <140/90 mmHg in individuals with diabetes and possibly <130/80 mmHg in individuals at increased risk for CVD and CKD progression.

Either ACE inhibitors or ARBs should be used to reduce the albuminuria and the associated decline in GFR in individuals with type 1 or type 2 DM (see "Hypertension," below). Most experts believe that the two classes of drugs are equivalent in patient with diabetes. ARBs can be used as an alternative in patients who develop ACE inhibitor–associated cough or angioedema. After initiation of therapy, some increase the dose and monitor the urinary albumin. There is no benefit of intervention prior to onset of albuminuria or using a combination of an ACE inhibitor and an ARB. If use of either ACE inhibitors or ARBs is not possible or the blood pressure is not controlled, then diuretics, calcium channel blockers (nondihydropyridine class), or beta blockers (with caution in individuals at increased risk for experiencing hypoglycemia) may be used. Mineralocorticoid receptor antagonists can help reduce blood pressure and albuminuria in refractory cases but require close monitoring of the serum potassium. SGLT-2 inhibitors can reduce albuminuria and, after an initial decline (~3 mL/min per 1.73 $m^2$) in GFR, may slow further decline in kidney function in individuals with and without T2DM and CKD. The mechanism of action of SGLT-2 inhibitors is multifactorial and includes inducing natriuresis, reducing intraglomerular pressure through restored tubuloglomerular feedback, and potentially altering signaling pathways related to nutrient sensing (e.g., AMPK). Because of the elevated risk of euglycemic diabetic ketoacidosis with SGLT-2 inhibitors, use in individuals with type 1 DM and insulin-deficient type 2 DM is not recommended. Some glucagon-like peptide-1 (GLP-1) receptor agonists may also both improve glycemic control and reduce the progression of diabetic kidney disease in individuals with type 2 DM and established CVD **(Chap. 404)**. The ADA suggests a protein intake of 0.8 mg/kg of body weight/day in individuals with diabetic kidney disease.

Nephrology consultation should be considered when the estimated GFR is <30 mL/min per 1.743 $m^2$ or with atypical features such as hematuria, rapidly declining renal function, or proteinuria > 3 g/day. Complications of atherosclerosis are the leading cause of death in diabetic individuals with nephropathy and hyperlipidemia should be treated aggressively. Referral for transplant evaluation should be made when the GFR approaches 20 mL/min per 1.73 $m^2$. Preemptive (before dialysis) kidney transplantation from a living donor or simultaneous pancreas-kidney transplantation from a deceased donor both offer improved patient and kidney survival over waiting for a deceased donor kidney alone. A combined pancreas-kidney transplant offers the promise of normoglycemia and freedom from both insulin and dialysis. As compared with nondiabetic individuals, hemodialysis in patients with DM is associated with more frequent complications, such as hypotension (due to autonomic neuropathy or loss of reflex tachycardia), more difficult vascular access, and accelerated progression of retinopathy.

## NEUROPATHY AND DIABETES MELLITUS

Diabetic neuropathy, which occurs in ~50% of individuals with long-standing type 1 and type 2 DM, manifests as a diffuse neuropathy (distal symmetrical polyneuropathy and/or autonomic neuropathy), a mononeuropathy, and/or a radiculopathy/polyradiculopathy. As with other complications of DM, the development of neuropathy correlates with the duration of diabetes and glycemic control. Additional risk factors are body mass index (BMI) (the greater the BMI, the greater the risk of neuropathy) and smoking. The presence of CVD, elevated triglycerides, and hypertension is also associated with diabetic peripheral neuropathy. Both myelinated and unmyelinated nerve fibers are lost. Because the clinical features of diabetic neuropathy are similar to those of other neuropathies, the diagnosis of diabetic neuropathy should be made only after other possible etiologies are excluded **(Chap. 446)**.

**Distal Symmetric Polyneuropathy (DSPN)** DSPN, the most common form of diabetic neuropathy, most frequently presents with distal sensory loss and pain, but up to 50% of patients do not have symptoms of neuropathy. Symptoms may include a sensation of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally. Hyperesthesia, paresthesia, and dysesthesia also may occur. Pain typically involves the lower extremities, is usually present at rest, and worsens at night. Both an acute (lasting <12 months) and a chronic form of painful diabetic neuropathy may occur. The acute form is sometimes treatment-related, occurring in the context of improved glycemic control. As diabetic neuropathy progresses, the pain subsides and eventually disappears, but a sensory deficit persists, and motor defects may develop. Physical examination **(Chap. 403)** often reveals sensory loss (to 10-g monofilament and/or vibration), loss of ankle deep-tendon reflexes, abnormal position sense, and muscular atrophy or foot drop. Annual screening for DSPN should begin 5 years after diagnosis of type 1 DM and at the time of diagnosis of type 2 DM and is aimed at detecting loss of protective sensation (LOPS). LOPS and DSPN are major risk factors for foot ulceration and falls due to small and large nerve fiber dysfunction and predispose to lower extremity amputation.

**Autonomic Neuropathy** Individuals with long-standing type 1 or 2 DM may develop signs of autonomic dysfunction involving the parasympathetic (cholinergic) and sympathetic (adrenergic) systems. DM-related autonomic neuropathy can affect multiple organ systems, including the cardiovascular, gastrointestinal (GI), genitourinary, sudomotor, and metabolic systems. Cardiovascular autonomic neuropathy, reflected by decreased heart rate variability, resting tachycardia, and orthostatic hypotension, is associated with an increase in CVD. Orthostatic hypotension, a late and unusual complication of diabetes, is sometimes seen in patients with associated DPN and severe parasympathetic dysfunction. Reports of sudden death in DM have also been attributed to autonomic neuropathy affecting the cardiovascular system and predisposing to severe hypoglycemia, both of which may prolong the QTc interval. Autonomic neuropathy may reduce counterregulatory hormone release (especially epinephrine), leading to an inability to sense hypoglycemia appropriately (hypoglycemia unawareness) **(Chap. 406)** and subjecting the patient to the risk of severe hypoglycemia. Gastroparesis and bladder-emptying abnormalities are often caused by the autonomic neuropathy seen in DM (discussed below). Hyperhidrosis of the upper extremities and anhidrosis of the lower extremities result from sympathetic nervous system dysfunction. Anhidrosis of the feet can promote dry skin with cracking, which increases the risk of foot ulcers.

**Mononeuropathy and/or Radiculopathy/Polyradiculopathy** Mononeuropathy (dysfunction of isolated cranial or peripheral nerves) is less common than polyneuropathy in DM and presents with pain

and motor weakness in the distribution of a single nerve. Mononeuropathies can occur at entrapment sites such as carpal tunnel or be noncompressive. Involvement of the third cranial nerve is most common and is heralded by diplopia. Physical examination reveals ptosis and ophthalmoplegia with normal pupillary constriction to light. Sometimes other cranial nerves, such as IV, VI, or VII (Bell's palsy), are affected. Peripheral mononeuropathies or simultaneous involvement of more than one nerve (mononeuropathy multiplex) may also occur. Diabetic radiculopathy or polyradiculopathy is a syndrome characterized by severe disabling pain in the distribution of one or more nerve roots. It may be accompanied by motor weakness. Intercostal or truncal radiculopathy causes pain over the thorax or abdomen. Involvement of the lumbar plexus or femoral nerve may cause severe pain in the thigh or hip and may be associated with muscle weakness in the hip flexors or extensors (diabetic amyotrophy). Fortunately, diabetic polyradiculopathies are usually self-limited and resolve over 6–12 months.

## TREATMENT

### Diabetic Neuropathy

Prevention of diabetic neuropathy is critical through improved glycemic control. Treatment of diabetic neuropathy is less than satisfactory. Lifestyle modifications (exercise, diet) have some efficacy in DSPN in type 2 DM and hypertension, and hypertriglyceridemia should be treated. Efforts to improve glycemic control in long-standing diabetes may be confounded by hypoglycemia unawareness. Patients should avoid neurotoxins (including alcohol) and smoking, and consider supplementation with vitamins for possible deficiencies ($B_{12}$, folate; **Chap. 333**). Metformin may reduce intestinal absorption of vitamin $B_{12}$ in type 2 DM, and pernicious anemia is more common in type 1 DM where it is associated with anti–parietal cell autoantibodies and may require sublingual or parenteral $B_{12}$ replacement. Patients should be educated that loss of sensation in the foot increases the risk for ulceration and its sequelae and that prevention of such problems is paramount. Patients with symptoms or signs of neuropathy or LOPS should check their feet daily and take precautions (footwear) aimed at preventing calluses or ulcerations. If foot deformities are present, a podiatrist should be involved.

Chronic, painful diabetic neuropathy is difficult to treat with only symptomatic treatment being available; evidence of the effectiveness of improved glycemic control in painful diabetic neuropathy is lacking. Two oral agents approved by the U.S. Food and Drug Administration (FDA), duloxetine and pregabalin, or gabapentin is usually initially used for pain associated with diabetic neuropathy. Diabetic neuropathy may respond to tricyclic antidepressants, venlafaxine, carbamazepine, tramadol, or topical capsaicin products. An 8% capsaicin patch requires application by a health care provider. Tapentadol, a centrally acting opioid, is also approved by the FDA, but has only modest efficacy and poses addiction risk, making it and other opioids less desirable and not a first-line therapy. No direct comparisons of agents are available, and it is reasonable to switch agents if there is no response or if side effects develop. Referral to a pain management center may be necessary.

Therapy of orthostatic hypotension secondary to autonomic neuropathy is also difficult. Nonpharmacologic maneuvers (adequate salt intake, avoidance of dehydration and diuretics, lower extremity support hose, and physical activity) may offer some benefit. A variety of agents have limited success (midodrine and droxidopa are approved by the FDA for orthostatic hypotension of any etiology). Patients with resting tachycardia may be considered for beta blocker therapy with caution exercised if there is hypoglycemia unawareness. Patients with type 1 DM and orthostatic hypotension should be evaluated for primary adrenal insufficiency (Addison's disease) that may be associated with anti-21-hydroxylase autoantibodies as part of an autoimmune polyendocrine syndrome **(Chap. 389)**.

## GASTROINTESTINAL/GENITOURINARY DYSFUNCTION

Long-standing type 1 and 2 DM may affect the motility and function of the GI and genitourinary systems. The most prominent GI symptoms are delayed gastric emptying (gastroparesis) and altered small- and large-bowel motility (constipation or diarrhea). Gastroparesis may present with symptoms of anorexia, nausea, vomiting, early satiety, and abdominal bloating. Microvascular complications (retinopathy and neuropathy) are usually present. Nuclear medicine scintigraphy after ingestion of a radiolabeled meal may document delayed gastric emptying but may not correlate well with the patient's symptoms. Noninvasive "breath tests" following ingestion of a radiolabeled meal are emerging as a diagnostic tool. Although parasympathetic dysfunction secondary to chronic hyperglycemia is important in the development of gastroparesis, hyperglycemia itself also impairs gastric emptying. Nocturnal diarrhea, alternating with constipation, is a feature of DM-related GI autonomic neuropathy. In type 1 DM, these symptoms should also prompt evaluation for celiac disease that is associated with anti-tissue transglutaminase autoantibodies because of its increased frequency.

Diabetic autonomic neuropathy may lead to genitourinary dysfunction including cystopathy and female sexual dysfunction (reduced sexual desire, dyspareunia, reduced vaginal lubrication). Symptoms of diabetic cystopathy begin with an inability to sense a full bladder and a failure to void completely. As bladder contractility worsens, bladder capacity and the postvoid residual increase, leading to symptoms of urinary hesitancy, decreased voiding frequency, incontinence, and recurrent urinary tract infections.

Erectile dysfunction and retrograde ejaculation are very common in DM and may be one of the earliest signs of diabetic neuropathy **(Chap. 397)**. Erectile dysfunction, which increases in frequency with the age of the patient and the duration of diabetes, may occur in the absence of other signs of diabetic autonomic neuropathy.

## TREATMENT

### Gastrointestinal/Genitourinary Dysfunction

Current treatments for these complications of DM are inadequate and nonspecific. Improved glycemic control should be a goal but has not clearly shown benefit. Smaller, more frequent meals that are easier to digest (liquid) and low in fat and fiber may minimize symptoms of gastroparesis. Medications that slow gastric emptying (opioids, GLP-1 receptor agonists) should be avoided. Metoclopramide may be used with severe symptoms but is restricted to short-term treatment in both the United States and Europe. Symptoms of gastroesophageal reflux disease may require acid blocking therapy with a histamine-2 receptor antagonist or proton pump inhibitor. Gastric electrical stimulatory devices are available but not approved. Diabetic diarrhea in the absence of bacterial overgrowth is treated symptomatically **(Chap. 325)**.

Diabetic cystopathy should be treated with scheduled voiding or self-catheterization. Drugs that inhibit type 5 phosphodiesterase are effective for erectile dysfunction, but their efficacy in individuals with DM is slightly lower than in the nondiabetic population **(Chap. 397)**.

## CARDIOVASCULAR MORBIDITY AND MORTALITY

CVD is increased in individuals with type 1 or type 2 DM. The Framingham Heart Study revealed a marked increase in PAD, coronary artery disease, MI, and CHF (risk increase from one- to fivefold) in DM. In addition, the prognosis for individuals with diabetes who have coronary artery disease or MI is worse than for nondiabetics. CHD is more likely to involve multiple vessels in individuals with DM. In addition to CHD, cerebrovascular disease is increased in individuals with DM (threefold increase in stroke). Thus, after controlling for all known cardiovascular risk factors, both type 1 and type 2 DM increases the cardiovascular death rate twofold in men and fourfold in women. CHF is common in long-standing DM.

The American Heart Association considers DM as a controllable risk factor for cardiovascular disease; in some studies, type 2 DM patients without a prior MI have a similar risk for coronary artery-related events as nondiabetic individuals who have had a prior MI. Cardiovascular risk assessment in type 2 DM should encompass a more nuanced approach. Cardiovascular risk is lower and not equivalent in a younger individual with a brief duration of type 2 DM compared to an older individual with long-standing type 2 DM. In individuals without a known diagnosis of diabetes, elevated $HbA_{1c}$ is predictive not just of diabetes risk but also risk of CHD, stroke, and all-cause mortality. Because of the extremely high prevalence of underlying CVD in individuals with diabetes (especially in type 2 DM), evidence of atherosclerotic vascular disease (e.g., cardiac stress test) should be sought in an individual with diabetes who has symptoms, even if atypical, suggestive of cardiac ischemia or peripheral or carotid arterial disease. The screening of asymptomatic individuals with diabetes for CHD is not recommended or cost-effective. The absence of chest pain ("silent ischemia") is common in individuals with diabetes, and a thorough cardiac evaluation should be considered prior to major surgical procedures.

The increase in cardiovascular morbidity and mortality rates in diabetes appears to relate to the synergism of hyperglycemia with other cardiovascular risk factors such as dyslipidemia (elevated triglycerides, low high-density lipoprotein [HDL] cholesterol and small dense low-density lipoprotein [LDL]), hypertension, obesity, reduced physical activity, and cigarette smoking. Additional risk factors that are prevalent include CKD (albuminuria, reduced GFR), abnormal platelet function, increased markers of inflammation, and endothelial dysfunction. The results of the ACCORD trial and VADT trial, which demonstrated that tight glucose control had limited benefit on cardiovascular outcomes in individuals with established cardiovascular disease, suggesting the importance of insulin resistance and dyslipidemia.

## TREATMENT

### Cardiovascular Disease

Treatment of coronary disease in individuals with DM has substantial overlap with treatment in individuals without DM **(Chap. 273)**. Revascularization procedures for CHD, including percutaneous coronary interventions (PCIs) and coronary artery bypass grafting (CABG), may be less efficacious in individuals with DM. Initial success rates of PCI in individuals with DM are similar to those in the nondiabetic population, but higher rates of restenosis and lower long-term patency and survival rates have been reported. CABG plus optimal medical management likely has better outcomes than PCI for individuals with diabetes.

Aggressive cardiovascular risk modification in all individuals with DM and glycemic control should be individualized, as discussed in **Chap. 404**. In patients with known CHD and type 2 DM, an ACE inhibitor or ARB, a statin, and acetylsalicylic acid (ASA; aspirin) should be considered. Beta blockers can be used in individuals with diabetes after MI. In patients with CHF, thiazolidinediones should not be used **(Chap. 404)**. However, metformin can be used in patients with stable CHF if the renal function is normal. Some newer glucose-lowering therapies also have cardiovascular benefit, including the GLP-1 analogues liraglutide (LEADER trial), semaglutide (SUSTAIN-6 trial), and dulaglutide (REWIND trial) and the SGLT-2 inhibitors empagliflozin (EMPA-REG trial) and canagliflozin (CANVAS trial). All SGLT-2 inhibitors have been shown to exhibit benefits on prevention of CHF exacerbations. A possible increased risk of lower limb amputation and Fournier's gangrene has been reported with SGLT-2 inhibitor therapy.

Antiplatelet therapy reduces cardiovascular events in individuals with DM who have CHD and is recommended. The ADA recommends considering the use of aspirin for primary prevention of coronary events in individuals with diabetes with an increased cardiovascular risk (>50 years old with at least one risk factor such as hypertension, dyslipidemia, smoking, family history, or albuminuria). ASA is not recommended for primary prevention in those with a low cardiovascular risk (<50 years old with no risk factors). The aspirin dose is the same as in nondiabetic individuals.

**Cardiovascular Risk Factors • DYSLIPIDEMIA** Individuals with DM may have several forms of dyslipidemia **(Chap. 407)**. Because of the additive cardiovascular risk of hyperglycemia and hyperlipidemia, lipid abnormalities should be assessed aggressively and treated as part of comprehensive diabetes care **(Chap. 404)**. The most common pattern of dyslipidemia is hypertriglyceridemia and reduced HDL cholesterol levels. DM itself does not increase levels of LDL, but the small dense LDL particles found in type 2 DM are more atherogenic because they are more easily glycated and susceptible to oxidation.

Almost all treatment studies of diabetic dyslipidemia have been performed in individuals with type 2 DM because of the greater frequency of dyslipidemia in this form of diabetes. Interventional studies have shown that the beneficial effects of LDL reduction with statins are similar in the diabetic and nondiabetic populations. No prospective studies have addressed similar questions in individuals with type 1 DM. Because the frequency of CVD is low in children and young adults with diabetes, assessment of cardiovascular risk should be incorporated into the guidelines discussed below.

Based on the guidelines provided by the ADA, all individuals with diabetes should be advised about lifestyle modification, including diet, weight loss, and increased physical activity **(Chap. 404)**. If individuals with diabetes have elevated triglyceride levels (>1.7 mmol/L [150 mg/dL]) or low HDL cholesterol (<1 mmol/L [40 mg/dL] in men and <1.3 mmol/L [50 mg/dL] in women), lifestyle modification and improved glycemic control should be further emphasized. If triglycerides remain >5.7 mmol/L (500 mg/dL), treatment with fish oil, fibrate drugs, and icosapent may reduce the risk of pancreatitis. Icosapent additionally lowers CHD risk.

In terms of pharmacologic therapy, the ADA recommends the following: (1) all patients with diabetes and atherosclerotic cardiovascular disease should receive high-intensity statin therapy; (2) in patients aged 40–75 years without cardiovascular disease, consider moderate-intensity statin therapy to target LDL cholesterol <100 mg/dL (without additional risk factors) or high-intensity statin therapy to target LDL cholesterol <70 mg/dL (with additional risk factors); and (3) in patients aged 20–39 years with additional risk factors, consider moderate-intensity statin therapy. Screening for coronary artery calcification by electron beam computed tomography (CT) scan that noninvasively detects the presence of coronary artery atherosclerosis may help guide treatment initiation or intensity in equivocal cases or ambivalent patients. Atorvastatin and rosuvastatin are generally well tolerated if started at lower doses and titrated up to meet lipid goals. Atorvastatin is the statin of choice in patients with renal disease. If statin intolerant or the LDL cholesterol goal is not met, consider the addition of ezetimibe or a PCSK9 inhibitor **(Chap. 407)**. Icosapent results in cardiovascular risk reduction on top of statin treatment and may have a larger benefit in diabetic individuals. Statin usage is associated with a mild increase in the risk of developing type 2 DM. This risk is greatest in individuals with other risk factors for type 2 DM **(Chap. 403)**. However, the cardiovascular benefits of statin use outweigh the mildly increased risk of diabetes. Niacin use is associated with an even greater increased risk for type 2 DM or worsening glycemic control and is not recommended because of a lack of improvement in cardiovascular outcomes.

In individuals with type 2 DM and kidney disease or type 2 DM and atherosclerotic cardiovascular disease or multiple atherosclerotic risk factors, the ADA recommends an SGLT-2 inhibitor or GLP-1 receptor agonist as a second-line agent after metformin. In individuals with type 2 DM and heart failure (reduced ejection fraction), the ADA recommends an SGLT-2 inhibitor. Individuals with atherosclerotic

cardiovascular disease and type 1 or type 2 DM should be treated with an ACE inhibitor or angiotensin receptor blocker and beta blockers and antiplatelet therapy, as in the nondiabetic population **(Chap. 273)**.

**HYPERTENSION** Hypertension can accelerate other complications of DM, particularly CVD, nephropathy, and retinopathy. Blood pressure should be measured at every clinic visit. In targeting a goal of blood pressure of <140/90 mmHg, therapy should first emphasize lifestyle modifications such as weight loss, exercise, stress management, and sodium restriction. The blood pressure goal should be individualized. In some younger individuals or those with increased cardiovascular risk, the provider may target a blood pressure of <130/80 mmHg. Realizing that more than one agent is usually required to reach the blood pressure goal, the ADA recommends that all patients with diabetes and hypertension be treated with an ACE inhibitor or an ARB initially. Subsequently, agents that reduce cardiovascular risk (beta blockers, thiazide diuretics, and calcium channel blockers) should be incorporated into the regimen. ACE inhibitors and ARBs are likely equivalent in most patients with diabetes and renal disease but should not be combined. The addition of a potassium-sparing diuretic or mineralocorticoid receptor antagonist can help achieve blood pressure targets in refractory cases. Serum potassium and renal function should be monitored.

Because of the high prevalence of atherosclerotic disease in individuals with type 2 DM, the possibility of renovascular hypertension should be considered when the blood pressure is not readily controlled.

## LOWER EXTREMITY COMPLICATIONS

DM is the leading cause of nontraumatic lower extremity amputation in the United States. Foot ulcers and infections are also a major source of morbidity in individuals with DM. The reasons for the increased incidence of these disorders in DM involve the interaction of several pathogenic factors: neuropathy, abnormal foot biomechanics, PAD, and poor wound healing. The peripheral sensory neuropathy interferes with normal protective mechanisms and allows the patient to sustain major or repeated minor trauma to the foot, often without knowledge of the injury. Disordered proprioception causes abnormal weight bearing while walking and subsequent formation of callus or ulceration. Motor and sensory neuropathy lead to abnormal foot muscle mechanics and to structural changes in the foot (hammer toe, claw toe deformity, prominent metatarsal heads, Charcot joint). Autonomic neuropathy results in anhidrosis and altered superficial blood flow in the foot, which promote drying of the skin and fissure formation. PAD and poor wound healing impede resolution of minor breaks in the skin, allowing them to enlarge and to become infected.

Many individuals with DM develop a foot ulcer (great toe or metatarsophalangeal areas are most common), and a significant subset who develop an ulceration will ultimately undergo amputation (14–24% risk with that ulcer or subsequent ulceration). Risk factors for foot ulcers or amputation include male sex, diabetes for >10 years, peripheral neuropathy, abnormal structure of foot (bony abnormalities, callus, thickened nails), PAD, smoking, history of previous ulcer or amputation, visual impairment, poor glycemic control, and diabetic nephropathy, especially dialysis. Large calluses are often precursors to or overlie ulcerations. Aggressive treatment of LDL cholesterol with the PCSK9 inhibitor evolocumab has been shown to reduce the risk of future major adverse limb events in patients with PAD.

## TREATMENT

### Lower Extremity Complications

The optimal therapy for foot ulcers and amputations is prevention through identification of high-risk patients, education of the patient, and institution of measures to prevent ulceration. High-risk patients should be identified during the routine, annual foot examination performed on all patients with DM (see "Ongoing Aspects of Comprehensive Diabetes Care" in **Chap. 404**). If the monofilament test or one of the other tests is abnormal, the patient is diagnosed with LOPS **(Chap. 403)**. Providers should consider screening for asymptomatic PAD in individuals >50 years of age who have diabetes and other risk factors using ankle-brachial index testing **(Chap. 281)**. Patient education should emphasize (1) careful selection of footwear, (2) daily inspection of the feet to detect early signs of poor-fitting footwear or minor trauma, (3) daily foot hygiene to keep the skin clean and moist, (4) avoidance of self-treatment of foot abnormalities and high-risk behavior (e.g., walking barefoot), and (5) prompt consultation with a health care provider if an abnormality arises. Calluses and nail deformities should be treated by a podiatrist. Interventions directed at risk factor modification include orthotic shoes and devices, callus management, nail care, and prophylactic measures to reduce increased skin pressure from abnormal bony architecture. Attention to other risk factors for vascular disease (smoking, dyslipidemia, hypertension) and improved glycemic control are also important.

Despite preventive measures, foot ulceration and infection are common and represent a serious problem. Due to the multifactorial pathogenesis of lower extremity ulcers, management of these lesions is multidisciplinary and often demands expertise in orthopedics, vascular surgery, endocrinology, podiatry, and infectious diseases. The plantar surface of the foot is the most common site of ulceration. Ulcers may be primarily neuropathic (no accompanying infection) or may have surrounding cellulitis or osteomyelitis. Cellulitis without ulceration should be treated with antibiotics that provide broad-spectrum coverage (see below).

An infected ulcer is a clinical diagnosis, because superficial culture of any ulceration will likely find multiple bacterial species of unknown significance. The infection surrounding the foot ulcer may be due to multiple organisms, with aerobic gram-positive cocci (staphylococci including methicillin-resistant *Staphylococcus aureus* [MRSA], group A and B streptococci) being most common and with aerobic gram-negative bacilli and/or obligate anaerobes as co-pathogens.

Gas gangrene may develop in the absence of clostridial infection. Cultures should be obtained from the debrided ulcer base or from purulent drainage or aspiration of the wound. Wound depth should be determined by inspection and probing with a blunt-tipped sterile instrument. A wound that probes to the bone represents clinical evidence of osteomyelitis. Plain radiographs of the foot should be performed to assess the possibility of osteomyelitis in chronic ulcers that have not responded to therapy. Magnetic resonance imaging (MRI) is the most specific modality, with nuclear medicine scans and labeled white cell studies as alternatives. Surgical debridement is often necessary.

Osteomyelitis is best treated by a combination of prolonged antibiotics and debridement of infected bone when possible. The possible contribution of vascular insufficiency should be considered in all patients. Peripheral arterial bypass procedures are often effective in promoting wound healing and in decreasing the need for amputation of the ischemic limb **(Chap. 281)**.

Interventions with demonstrated efficacy in diabetic foot ulcers or wounds include the following: (1) off-loading, (2) debridement, (3) wound dressings, (4) appropriate use of antibiotics, (5) revascularization, and (6) limited amputation. Off-loading is the complete avoidance of weight bearing on the ulcer, which removes the mechanical trauma that retards wound healing. Bed rest and a variety of orthotic devices or contact casting limit weight bearing on wounds or pressure points. Surgical debridement is important and effective, but the efficacy of other modalities for wound healing (enzymes, growth factors, cellular therapy, hyperbaric oxygen) is unclear. Dressings such as hydrocolloid dressings promote wound healing by creating a moist environment, controlling the exudate, and protecting the wound. Antiseptic agents should be avoided. Topical antibiotics are of limited value. Referral for physical therapy, orthotic evaluation, and rehabilitation should occur once the infection is controlled.

Mild or non-limb-threatening infections can be treated with oral antibiotics directed predominantly at methicillin-susceptible staphylococci and streptococci (e.g., dicloxacillin, cephalosporin, amoxicillin/clavulanate). However, in patients with a prior history of MRSA or in locations with a high prevalence of MRSA, treatment with clindamycin, doxycycline, or trimethoprim-sulfamethoxazole is preferred. Trimethoprim-sulfamethoxazole exhibits less reliable coverage of streptococci than the β-lactams, and individuals with diabetes may develop adverse effects including acute kidney injury and hyperkalemia. Surgical debridement of necrotic tissue, local wound care (avoidance of weight bearing over the ulcer), and close surveillance for progression of infection are crucial. More severe infections require IV antibiotics as well as offloading and local wound care. Urgent surgical debridement may be required. Optimization of glycemic control should be a goal. IV antibiotics should provide broad-spectrum coverage directed toward *S. aureus*, including MRSA, streptococci, gram-negative aerobes, and anaerobic bacteria. Initial antimicrobial regimens include vancomycin plus a β-lactam/β-lactamase inhibitor or carbapenem, or vancomycin plus a quinolone with metronidazole. In some cases, daptomycin, ceftaroline, or linezolid may be substituted for vancomycin in consultation with an Infectious Diseases expert. If the infection surrounding the ulcer is not improving with IV antibiotics, reassessment of antibiotic coverage and reconsideration of the need for surgical debridement or revascularization are indicated. With clinical improvement, oral antibiotics and local wound care can be continued on an outpatient basis with close follow-up.

## INFECTIONS

Individuals with DM have a greater frequency and severity of infection. The reasons for this include incompletely defined abnormalities in cell-mediated immunity and phagocyte function associated with hyperglycemia, as well as diminished vascularization. Hyperglycemia aids the colonization and growth of a variety of organisms (*Candida* and other fungal species). Many common infections are more frequent and severe in the diabetic population, whereas several rare infections are seen almost exclusively in the diabetic population. Examples of this latter category include rhinocerebral mucormycosis, emphysematous infections of the gallbladder and urinary tract, and "malignant" or invasive otitis externa. Invasive otitis externa is usually secondary to *Pseudomonas aeruginosa* infection in the soft tissue surrounding the external auditory canal, usually begins with pain and discharge, and may rapidly progress to osteomyelitis and meningitis. These infections should be sought, in particular, in patients presenting with severe hyperglycemia **(Chap. 404)**.

Pneumonia, urinary tract infections, and skin and soft tissue infections are all more common in the diabetic population. In general, the organisms that cause pulmonary infections are similar to those found in the nondiabetic population; however, gram-negative organisms, *S. aureus*, and *Mycobacterium tuberculosis* are more frequent pathogens. Adults with DM should receive vaccination against pneumococcus, annually against influenza, and now also against the coronavirus SARS-CoV-2, which causes increased morbidity and mortality in obese individuals and patients with DM **(Chap. 199)**. In addition to early antibiotic therapy for presumed bacterial infections, patients with DM should be considered for early intervention with antiviral agents (e.g., against influenza in flu or varicella-zoster virus in shingles) or with monoclonal antibodies in COVID-19. Urinary tract infections (either lower tract or pyelonephritis) are the result of common bacterial agents such as *Escherichia coli*, although several yeast species (e.g., *Candida albicans* and *Candida glabrata*) are commonly observed. Complications of urinary tract infections include emphysematous pyelonephritis and emphysematous cystitis. Bacteriuria occurs frequently in individuals with diabetic cystopathy and does not require antibiotic therapy except in specific circumstances such as pregnancy or a planned urologic procedure. Susceptibility to furunculosis, superficial candidal infections, and vulvovaginitis are increased. Poor glycemic control is a common denominator in individuals with these infections. Individuals with diabetes have an increased rate of colonization of *S. aureus* in the skinfolds and nares. Individuals with diabetes also have a greater risk of postoperative wound infections that may be mitigated by perioperative protocols for insulin administration to maintain glycemic control.

## DERMATOLOGIC MANIFESTATIONS

The most common skin manifestations of DM are xerosis and pruritus and are usually relieved by skin moisturizers. Protracted wound healing and skin ulcerations are also frequent complications. Diabetic dermopathy, sometimes termed *pigmented pretibial papules*, or "diabetic skin spots," begins as an erythematous macule or papule that evolves into an area of circular hyperpigmentation. These lesions result from minor mechanical trauma in the pretibial region and are more common in elderly men with DM. Bullous diseases, such as bullosa diabeticorum (shallow ulcerations or erosions in the pretibial region), are also seen. *Necrobiosis lipoidica diabeticorum* is an uncommon disorder, accompanying diabetes in predominantly young women. This usually begins in the pretibial region as an erythematous plaque or papules that gradually enlarge, darken, and develop irregular margins, with atrophic centers and central ulceration. They are often painful. Vitiligo and alopecia areata occur at increased frequency in individuals with type 1 DM. *Acanthosis nigricans* (hyperpigmented velvety plaques seen on the neck, axilla, or extensor surfaces) is sometimes a feature of severe insulin resistance and accompanying diabetes. Generalized or localized *granuloma annulare* (erythematous plaques on the extremities or trunk), *lichen planus* (violaceous papules on the cutaneous surface with or without erosions in the mouth and genitalia), and *scleredema* (areas of skin thickening on the back or neck at the site of previous superficial infections) are more common in the diabetic population. *Lipoatrophy* and *lipohypertrophy* can occur at insulin injection sites but are now unusual with the use of human insulin and avoided by rotating injection sites.

## FURTHER READING


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