DIABETES MELLITUS: INTRODUCTION

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. It also predisposes to cardiovascular diseases. With an increasing incidence worldwide, DM will be a leading cause of morbidity and mortality for the foreseeable future.
CLASSIFICATION

DM is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy (Fig. 344-1). The two broad categories of DM are designated type 1 and type 2 (Table 344-1). Both types of diabetes are preceded by a phase of abnormal glucose homeostasis as the pathogenic processes progress. Type 1 DM is the result of complete or near-total insulin deficiency. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Distinct genetic and metabolic defects in insulin action and/or secretion give rise to the common phenotype of hyperglycemia in type 2 DM and have important potential therapeutic implications now that pharmacologic agents are available to target specific metabolic derangements. Type 2 DM is preceded by a period of abnormal glucose homeostasis classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).

**Figure 344-1**

<table>
<thead>
<tr>
<th>Type of Diabetes</th>
<th>Normal glucose tolerance</th>
<th>Pre-diabetes*</th>
<th>Diabetes Mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td></td>
<td>Impaired fasting glucose or impaired glucose tolerance</td>
<td>Not insulin requiring for control</td>
</tr>
<tr>
<td>Type 2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Other specific types</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gestational Diabetes</td>
<td></td>
<td></td>
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<tr>
<td>Time (years)</td>
<td></td>
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<tr>
<td>FPG</td>
<td>&lt;5.6 mmol/L (100 mg/dL)</td>
<td>5.6–6.9 mmol/L (100–125 mg/dL)</td>
<td>≥7.0 mmol/L (126 mg/dL)</td>
</tr>
<tr>
<td>2-h PG</td>
<td>&lt;7.8 mmol/L (140 mg/dL)</td>
<td>7.8–11.0 mmol/L (140–199 mg/dL)</td>
<td>≥11.1 mmol/L (200 mg/dL)</td>
</tr>
<tr>
<td>A1C</td>
<td>&lt;5.6%</td>
<td>5.7–6.4%</td>
<td>≥6.5%</td>
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Spectrum of glucose homeostasis and diabetes mellitus (DM). The spectrum from normal glucose tolerance to diabetes in type 1 DM, type 2 DM, other specific types of diabetes, and gestational DM is shown from left to right. 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). Arrows indicate that 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 even normal glucose tolerance after delivery. The fasting plasma glucose (FPG), the 2-h plasma glucose (PG) after a glucose challenge, and the A1C for the different categories of glucose tolerance are shown at the lower part of the figure. These values do not apply to the diagnosis of gestational DM. The World Health Organization uses an FPG of 110–125 mg/dL for the prediabetes category. Some types of DM may or may not require insulin for survival. *Some use the term "increased risk for diabetes" (ADA) or "intermediate hyperglycemia" (WHO) rather than "prediabetes." (Adapted from the American Diabetes Association, 2007.)

Table 344-1 Etiologic Classification of Diabetes Mellitus

<table>
<thead>
<tr>
<th>I. Type 1 diabetes (beta cell destruction, usually leading to absolute insulin deficiency)</th>
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</thead>
<tbody>
<tr>
<td>A. Immune-mediated</td>
</tr>
<tr>
<td>B. Idiopathic</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>III. Other specific types of diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Genetic defects of beta cell function characterized by mutations in:</td>
</tr>
<tr>
<td>1. Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1)</td>
</tr>
<tr>
<td>2. Glucokinase (MODY 2)</td>
</tr>
<tr>
<td>3. HNF-1α (MODY 3)</td>
</tr>
<tr>
<td>4. Insulin promoter factor-1 (IPF-1; MODY 4)</td>
</tr>
<tr>
<td>5. HNF-1β (MODY 5)</td>
</tr>
<tr>
<td>6. NeuroD1 (MODY 6)</td>
</tr>
<tr>
<td>7. Mitochondrial DNA</td>
</tr>
<tr>
<td>8. Subunits of ATP-sensitive potassium channel</td>
</tr>
<tr>
<td>9. Proinsulin or insulin</td>
</tr>
<tr>
<td>B. Genetic defects in insulin action</td>
</tr>
<tr>
<td>1. Type A insulin resistance</td>
</tr>
<tr>
<td>2. Leprechaunism</td>
</tr>
<tr>
<td>3. Rabson-Mendenhall syndrome</td>
</tr>
<tr>
<td>4. Lipodystrophy syndromes</td>
</tr>
<tr>
<td>C. Diseases of the exocrine pancreas—pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, mutations in carboxyl ester lipase</td>
</tr>
</tbody>
</table>
D. Endocrinopathies—acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma

E. Drug- or chemical-induced—glucocorticoids, vacor (a rodenticide), pentamidine, nicotinic acid, diazoxide, β-adrenergic agonists, thiazides, hydantoins, asparaginase, α-interferon, protease inhibitors, antipsychotics (atypicals and others), epinephrine

F. Infections—congenital rubella, cytomegalovirus, coxsackievirus

G. Uncommon forms of immune-mediated diabetes— "stiff-person" syndrome, anti-insulin receptor antibodies


IV. Gestational diabetes mellitus (GDM)

Abbreviation: MODY, maturity-onset diabetes of the young.

Source: Adapted from American Diabetes Association, 2011.

Two features of the current classification of DM diverge from previous classifications. First, the terms insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) are obsolete. Since many individuals with type 2 DM eventually require insulin treatment for control of glycemia, the use of the term NIDDM generated considerable confusion. A second difference is that age is not a criterion in the classification system. Although type 1 DM most commonly develops before the age of 30, an autoimmune beta cell destructive process can develop at any age. It is estimated that between 5 and 10% of individuals who develop DM after age 30 years have type 1 DM. Although type 2 DM more typically develops with increasing age, it is now being diagnosed more frequently in children and young adults, particularly in obese adolescents.

Other Types of DM

Other etiologies for 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 344-1). Maturity-onset diabetes of the young (MODY) is a subtype of DM characterized by autosomal dominant inheritance, early onset of hyperglycemia (usually <25 years), and impairment in insulin secretion (discussed below). Mutations in the insulin receptor cause a group of rare disorders characterized by severe insulin resistance.

DM can result from pancreatic exocrine disease when the majority of pancreatic islets are destroyed. Cystic fibrosis-related DM is an important consideration in this patient population. Hormones that antagonize insulin action can also lead to DM. Thus, DM 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 islets.

Gestational Diabetes Mellitus (GDM)

Glucose intolerance developing during pregnancy is classified as gestational diabetes. Insulin resistance is related to the metabolic changes of late pregnancy, and the increased insulin requirements may lead to IGT or diabetes. GDM occurs in ~7% (range 2–10%) of pregnancies in the United States; most
women revert to normal glucose tolerance postpartum but have a substantial risk (35–60%) of developing DM in the next 10–20 years. The International Diabetes and Pregnancy Study Groups now recommends that diabetes diagnosed at the initial prenatal visit should be classified as "overt" diabetes rather than gestational diabetes.
EPIDEMIOLOGY

The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 285 million in 2010. Based on current trends, the International Diabetes Federation projects that 438 million individuals will have diabetes by the year 2030 (Fig. 344-2). 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 increasing obesity, reduced activity levels as countries become more industrialized, and the aging of the population. In 2010, the prevalence of diabetes ranged from 11.6 to 30.9% in the 10 countries with the highest prevalence (Naurua, United Arab Emirates, Saudi Arabia, Mauritius, Bahrain, Reunion, Kuwait, Oman, Tonga, Malaysia—in descending prevalence; Fig. 344-2). In the most recent estimate for the United States (2010), the Centers for Disease Control and Prevention (CDC) estimated that 25.8 million persons, or 8.3% of the population, had diabetes (~27% of the individuals with diabetes were undiagnosed). Approximately 1.6 million individuals (>20 years) were newly diagnosed with diabetes in 2010. DM increases with aging. In 2010, the prevalence of DM in the United States was estimated to be 0.2% in individuals aged <20 years and 11.3% in individuals aged >20 years. In individuals aged >65 years, the prevalence of DM was 26.9%. The prevalence is similar in men and women throughout most age ranges (11.8% and 10.8%, respectively, in individuals aged >20 years). Worldwide estimates project that in 2030 the greatest number of individuals with diabetes will be aged 45–64 years.

Figure 344-2

There is considerable geographic variation in the incidence of both type 1 and type 2 DM. Scandinavia has the highest incidence of type 1 DM (e.g., in Finland, the incidence is 57.4/100,000 per year). The Pacific Rim has a much lower rate of type 1 DM (in Japan and China, the incidence is 0.6–2.4/100,000 per year); Northern Europe and the United States have an intermediate rate (8–20/100,000 per year). 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. 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. For example, the CDC estimated that the age-adjusted prevalence of DM in the United States (age > 20 years; 2007–2009) was 7.1% in non-Hispanic whites, 7.5% in Asian Americans, 11.8% in Hispanics, and 12.6% in non-Hispanic blacks. Comparable statistics for individuals belonging to American Indian, Alaska Native, or Pacific-Islander ethnic groups are not available, but the prevalence likely exceeds the rate in non-Hispanic whites. 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 and the diabetes phenotype appears to be different from that in the United States and Europe—onset at a lower BMI and younger age, greater visceral adiposity, and reduced insulin secretory capacity.

Diabetes is a major cause of mortality, but several studies indicate that diabetes is likely underreported as a cause of death. In the United States, diabetes was listed as the seventh leading cause of death in 2007; a recent estimate suggested that diabetes was the fifth leading cause of death worldwide and was responsible for almost 4 million deaths in 2010 (6.8% of deaths were attributed to diabetes worldwide).
DIAGNOSIS

Glucose tolerance is classified into three broad categories: normal glucose homeostasis, diabetes mellitus, and impaired glucose homeostasis. Glucose tolerance can be assessed using the fasting plasma glucose (FPG), the response to oral glucose challenge, or the hemoglobin A1C (A1C). An FPG <5.6 mmol/L (100 mg/dL), a plasma glucose <140 mg/dL (11.1 mmol/L) following an oral glucose challenge, and an A1C <5.6% are considered to define normal glucose tolerance. The International Expert Committee with members appointed by the American Diabetes Association, the European Association for the Study of Diabetes, and the International Diabetes Federation has issued diagnostic criteria for DM (Table 344-2) based on the following premises: (1) the FPG, the response to an oral glucose challenge (OGTT—oral glucose tolerance test), and A1C differ among individuals, and (2) DM is defined as the level of glycemia at which diabetes-specific complications occur rather than on deviations 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. 344-3).

Table 344-2 Criteria for the Diagnosis of Diabetes Mellitus

- Symptoms of diabetes plus random blood glucose concentration ≥ 11.1 mmol/L (200 mg/dL)a or
- Fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL)b or
- A1C > 6.5%c or
- Two-hour plasma glucose ≥ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance testd

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 The test should be performed in laboratory certified according to A1C standards of the Diabetes Control and Complications Trial.
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.

Note: In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

Source: American Diabetes Association, 2011.
Figure 344-3

![Graph showing relationship of diabetes-specific complication and glucose tolerance.](image)

**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 A1C. Note that the incidence of retinopathy greatly increases at a fasting plasma glucose >116 mg/dL, or a 2-h plasma glucose of 185 mg/dL, or an A1C > 6.5%. (Blood glucose values are shown in mg/dL; to convert to mmol/L, divide value by 18.) (Copyright 2002, American Diabetes Association. From Diabetes Care 25(Suppl 1): S5–S20, 2002.)

An 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 A1C ≥6.5% warrant the diagnosis of DM (Table 344-2). A random plasma glucose concentration ≥11.1 mmol/L (200 mg/dL) accompanied by classic symptoms of DM (polyuria, polydipsia, weight loss) also is sufficient for the diagnosis of DM (Table 344-2).

Abnormal glucose homeostasis (Fig. 344-1) is defined as (1) FPG = 5.6–6.9 mmol/L (100–125 mg/dL), which is defined as IFG (note that the World Health Organization uses an FPG of 6.1–6.9 mmol/L (110–125 mg/dL); (2) plasma glucose levels between 7.8 and 11 mmol/L (140 and 199 mg/dL) following an oral glucose challenge, which is termed impaired glucose tolerance (IGT); or (3) A1C of 5.7–6.4%. An A1C of 5.7–6.4%, IFG, and IGT do not identify the same individuals, but individuals in all three groups are at greater risk of progressing to type 2 diabetes and have an increased risk of cardiovascular disease. Some use the term "prediabetes," "increased risk of diabetes" (ADA), or "intermediate hyperglycemia" (WHO) for this category. The current criteria for the diagnosis of DM emphasize that the A1C or the FPG as the most reliable and convenient tests for identifying DM in asymptomatic individuals. Oral glucose tolerance testing, although still a valid means for diagnosing DM, is not often used in routine clinical care.
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 (Table 344-2). 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 A1C 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, and (4) treatment of type 2 DM may favorably alter the natural history of DM. The ADA recommends screening all individuals >45 years every 3 years and screening individuals at an earlier age if they are overweight [body mass index (BMI) >25 kg/m²] and have one additional risk factor for diabetes (Table 344-3). In contrast to type 2 DM, a long asymptomatic period of hyperglycemia is rare prior to the diagnosis of type 1 DM. A number of immunologic markers for type 1 DM are becoming available (discussed below), but their routine use is discouraged pending the identification of clinically beneficial interventions for individuals at high risk for developing type 1 DM.

<table>
<thead>
<tr>
<th><strong>Table 344-3 Risk Factors for Type 2 Diabetes Mellitus</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of diabetes (i.e., parent or sibling with type 2 diabetes)</td>
</tr>
<tr>
<td>Obesity (BMI ≥25 kg/m²)</td>
</tr>
<tr>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)</td>
</tr>
<tr>
<td>Previously identified with IFG, IGT, or an A1C of 5.7–6.4%</td>
</tr>
<tr>
<td>History of GDM or delivery of baby &gt;4 kg (9 lb)</td>
</tr>
<tr>
<td>Hypertension (blood pressure ≥140/90 mmHg)</td>
</tr>
<tr>
<td>HDL cholesterol level &lt;35 mg/dL (0.90 mmol/L) and/or a triglyceride level &gt;250 mg/dL (2.82 mmol/L)</td>
</tr>
<tr>
<td>Polycystic ovary syndrome or acanthosis nigricans</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
</tr>
</tbody>
</table>

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

**Source:** Adapted from American Diabetes Association, 2011.
INSULIN BIOSYNTHESIS, SECRETION, AND ACTION

Biosynthesis

Insulin is produced in the beta cells of the pancreatic islets. It 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 the C peptide and the A (21 amino acids) and B (30 amino acids) chains of insulin, which are 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. 345 and 350). 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. Human insulin is produced by recombinant DNA technology; structural alterations at one or more amino acid residues modify its physical and pharmacologic characteristics (see below).

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, 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. 344-4). 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., sulfonyl-ureas, 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 secretory profiles reveal a pulsatile pattern of hormone release, with small secretory bursts occurring about every 10 min, superimposed upon greater amplitude oscillations of about 80–150 min. Incretins are released from neuroendocrine cells of the gastrointestinal tract following food ingestion and amplify glucose-stimulated insulin secretion and suppress glucagon secretion. Glucagon-like peptide 1 (GLP-1), the most potent incretin, is released from L cells in the small intestine and stimulates insulin secretion only when the blood glucose is above the fasting level. Incretin analogues, are used to enhance endogenous insulin secretion (see below).

Figure 344-4
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 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 maturity-onset diabetes of the young (MODY) or other forms of diabetes. SUR, sulfonylurea receptor; ATP, adenosine triphosphate; ADP, adenosine diphosphate, cAMP, cyclic adenosine monophosphate. IAPP, islet amyloid polypeptide or amylin.

Action

Once insulin is secreted into the portal venous system, ~50% is removed and degraded by the liver. Unextracted insulin enters the systemic circulation where it binds to receptors in target sites. Insulin binding to its receptor stimulates intrinsic tyrosine kinase activity, leading to receptor autophosphorylation and the recruitment of intracellular signaling molecules, such as insulin receptor substrates (IRS) (Fig. 344-5). 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.

Figure 344-5
Insulin signal transduction pathway in skeletal muscle. The insulin receptor has intrinsic tyrosine kinase activity and interacts with insulin receptor substrates (IRS and Shc) proteins. A number of “docking” proteins bind to these cellular proteins and initiate the metabolic actions of insulin [GrB-2, SOS, SHP-2, p110, and phosphatidylinositol-3′-kinase (PI-3-kinase)]. Insulin increases glucose transport through PI-3-kinase and the Cbl pathway, which promotes the translocation of intracellular vesicles containing GLUT4 glucose transporter to the plasma membrane.

Glucose homeostasis reflects a balance between hepatic glucose production and peripheral 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 (Chap. 345; see Fig. 345-1). In the fasting state, low insulin levels increase glucose production by promoting hepatic gluconeogenesis and glycogenolysis and reduce glucose uptake in insulin-sensitive tissues (skeletal muscle and fat), thereby promoting mobilization of stored precursors such as amino acids and free fatty acids (lipolysis). Glucagon, secreted by pancreatic alpha cells when blood glucose or insulin levels are low, stimulates glycogenolysis and gluconeogenesis by the liver and renal medulla. Postprandially, the glucose load elicits a rise in insulin and fall in glucagon, leading to a reversal of these processes. 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.
**PATHOGENESIS**

**Type 1 DM**

Type 1 DM is the result of interactions of genetic, environmental, and immunologic factors that ultimately lead to the destruction of the pancreatic beta cells and insulin deficiency. Type 1 DM results from autoimmune beta cell destruction, and most, but not all, individuals have evidence of islet-directed autoimmunity. Some individuals who have the clinical phenotype of type 1 DM lack immunologic markers indicative of an autoimmune process involving the beta cells and the genetic markers of type 1 diabetes. These individuals are thought to develop insulin deficiency by unknown, nonimmune mechanisms and are ketosis prone; many are African American or Asian in heritage. The temporal development of type 1 DM is shown schematically as a function of beta cell mass in **Fig. 344-6**.

Individuals with a genetic susceptibility have normal beta cell mass at birth but begin to lose beta cells secondary to autoimmune destruction that occurs over months to years. This autoimmune process is thought to be triggered by an infectious or environmental stimulus and to be sustained by a beta cell–specific molecule. In the majority, immunologic markers appear after the triggering event but before diabetes becomes clinically overt. Beta cell mass then begins to decrease, and insulin secretion progressively declines, although normal glucose tolerance is maintained. The rate of decline in beta cell mass varies widely among individuals, with some patients progressing rapidly to clinical diabetes and others evolving more slowly. Features of diabetes do not become evident until a majority of beta cells are destroyed (70–80%). At this point, residual functional beta cells exist but are insufficient in number 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 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 as the autoimmune process destroys remaining beta cells, and the individual becomes insulin deficient. Some individuals with long-standing type 1 diabetes produce a small amount of insulin (as reflected by C-peptide production) and some individuals have insulin-positive cells in the pancreas at autopsy.

**Figure 344-6**
Temporal model for development of type 1 diabetes. Individuals with a genetic predisposition are exposed to an immunologic trigger that initiates an autoimmune process, resulting in a gradual decline in beta cell mass. The downward slope of the beta cell mass varies among individuals and may not be continuous. This progressive impairment in insulin release results in diabetes when ~80% of the beta cell mass is destroyed. 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. [Adapted from Medical Management of Type 1 Diabetes, 3rd ed, JS Skyler (ed). American Diabetes Association, Alexandria, VA, 1998.]

Genetic Considerations

Susceptibility to type 1 DM involves multiple genes. The concordance of type 1 DM in identical twins ranges between 40 and 60%, 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 40–50% 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. 315). 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.

Most 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 normal U.S. population. However, most individuals with predisposing haplotypes do not develop diabetes.

In addition to MHC class II associations, genome association studies have identified at least 20 different genetic loci that contribute susceptibility to type 1 DM (polymorphisms in the promoter region of the insulin gene, the CTLA-4 gene, interleukin-2 receptor, CTLA4, and PTPN22, etc.). 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 tenfold in relatives of individuals with the disease, the risk is relatively low: 3–4% if the parent has type 1 diabetes and 5–15% in a sibling (depending on which HLA haplotypes are shared). Hence, most individuals with type 1 DM do not have a first-degree relative with this disorder.

**PATHOPHYSIOLOGY**

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 and express most of the same proteins as beta cells, they are spared from the autoimmune destruction. Pathologically, the pancreatic islets are infiltrated with lymphocytes (a process termed **insulitis**). After all beta cells are destroyed, the inflammatory process abates, the islets become atrophic, and most immunologic markers disappear. Studies of the autoimmune process in humans and in animal models of type 1 DM (NOD mouse and BB rat) have identified the following abnormalities in the humoral and cellular arms of the immune system: (1) islet cell autoantibodies; (2) activated lymphocytes in the islets, peripancreatic lymph nodes, and systemic circulation; (3) T lymphocytes that proliferate when stimulated with islet proteins; and (4) release of cytokines within the insulitis. Beta cells seem to be particularly susceptible to the toxic effect of some cytokines [tumor necrosis factor \( \alpha \) (TNF-\( \alpha \)), interferon \( \gamma \), and interleukin 1 (IL-1)]. The precise mechanisms of beta cell death are not known but may involve formation of nitric oxide metabolites, apoptosis, and direct CD8+ T cell cytotoxicity. The islet destruction is mediated by T lymphocytes rather than islet autoantibodies, as these antibodies do not generally react with the cell surface of islet cells and are not capable of transferring DM to animals. Suppression of the autoimmune process at the time of diagnosis of diabetes slows the decline in beta cell destruction, but the safety of such interventions is unknown.

Pancreatic islet molecules targeted by the autoimmune process include insulin, glutamic acid decarboxylase (GAD, the biosynthetic enzyme for the neurotransmitter GABA), ICA-512/IA-2 (homology with tyrosine phosphatases), and a beta cell–specific zinc transporter (ZnT-8). Most of the autoantigens are not beta cell–specific, which raises the question of how the beta cells are selectively destroyed. Current theories favor initiation of an autoimmune process directed at one beta cell molecule, which then spreads to other islet molecules as the immune process destroys beta cells and creates a series of secondary autoantigens. The beta cells of individuals who develop type 1 DM do not differ from beta cells of normal individuals, since islets transplanted from a genetically identical twin are destroyed by a recurrence of the autoimmune process of type 1 DM.

**IMMUNOLOGIC MARKERS**

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. Assays for autoantibodies to GAD-65 are commercially available. Testing for ICAs can be useful in classifying the type of DM as type 1 and in identifying nondiabetic individuals at risk for developing type 1 DM. ICAs are present in the majority of individuals (>85%) diagnosed with new-onset type 1 DM, in a significant minority of individuals with newly diagnosed type 2 DM (5–10%), and occasionally in individuals with GDM (<5%). ICAs are present in 3–4% of first-degree relatives of individuals with type 1 DM. In combination with impaired insulin secretion after IV glucose tolerance testing, they predict a >50% risk of developing type 1 DM within 5 years. At present, the measurement of ICAs in nondiabetic individuals is a research tool because no treatments have been approved to prevent the occurrence or progression to type 1 DM. Clinical trials are testing interventions to slow the autoimmune beta cell destruction.

ENVIRONMENTAL FACTORS

Numerous environmental events have been proposed to trigger the autoimmune process in genetically susceptible individuals; however, none have 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. 344-6). Putative environmental triggers include viruses (coxsackie, rubella, enteroviruses most prominently), bovine milk proteins, and nitrosourea compounds.

PREVENTION OF TYPE 1 DM

A number of interventions have successfully delayed or prevented diabetes in animal models. Some interventions have targeted the immune system directly (immunosuppression, selective T cell subset deletion, induction of immunologic tolerance to islet proteins), whereas others have prevented islet cell death by blocking cytotoxic cytokines or increasing islet resistance to the destructive process. Though results in animal models are promising, these interventions have not been successful in preventing type 1 DM in humans. The Diabetes Prevention Trial—type 1 concluded that administering insulin (IV or PO) to individuals at high risk for developing type 1 DM did not prevent type 1 DM.

In patients with new-onset type 1 diabetes, treatment with anti-CD3 monoclonal antibodies, a GADvaccine, and anti-B lymphocyte monoclonal antibody have been shown to slow the decline in C-peptide levels. This is an area of active clinical investigation.

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 common phenotype of hyperglycemia. Most of our current understanding (and the discussion below) of the pathophysiology and genetics is based on studies of individuals of European descent. It is becoming increasing apparent that DM in other ethnic groups (Asian, African, and Latin American) has a different, but yet undefined, pathophysiology. In these groups, DM that is ketosisprone (often obese) or ketosis-resistant (often lean) is commonly seen.

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 40%. 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, since in addition to genetic susceptibility, environmental factors (such as obesity, nutrition, and physical activity) modulate the phenotype. The genes that predispose to type 2 DM are incompletely identified, but recent genome-wide association studies have identified a large number of genes that convey a relatively small risk for type 2 DM (20 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 type 2 diabetes in several populations and with impaired glucose tolerance in one population at high risk for diabetes. Genetic polymorphisms associated with type 2 diabetes have also been found in the genes encoding the peroxisome proliferators-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 diabetes are not clear, but most are predicted to alter islet function or development or insulin secretion. While the genetic susceptibility to type 2 diabetes is under active investigation (estimation 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 predict type 2 diabetes.

PATHOPHYSIOLOGY

Type 2 DM is characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production, and abnormal fat metabolism. Obesity, particularly visceral or central (as evidenced by the hip-waist ratio), is very common in type 2 DM (80% or more 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. 344-7). As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state. IGT, characterized by elevations in postprandial glucose, then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Ultimately, beta cell failure ensues.

**Figure 344-7**
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). (Adapted from SE Kahn: J Clin Endocrinol Metab 86:4047, 2001; RN Bergman, M Ader: Trends Endocrinol Metab 11:351, 2000.)

**METABOLIC ABNORMALITIES**

**Abnormal Muscle and Fat Metabolism**

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 and obesity. Insulin resistance is relative, however, since supranormal levels of circulating insulin will normalize the plasma glucose. Insulin dose-response curves exhibit a rightward shift, indicating reduced sensitivity, and a reduced maximal response, indicating an overall decrease in maximum glucose utilization (30–60% lower than in normal individuals). Insulin resistance impairs glucose utilization by insulin-sensitive tissues and increases hepatic glucose output; both effects contribute to the hyperglycemia. Increased hepatic glucose output predominantly accounts for increased FPG levels, whereas decreased peripheral glucose usage results in postprandial hyperglycemia. In skeletal muscle, there is a greater impairment in nonoxidative glucose usage (glycogen formation) than in oxidative glucose metabolism through glycolysis. Glucose metabolism in insulin-independent tissues is not altered in type 2 DM.

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 (Fig. 344-5). For example, a PI-3-kinase signaling defect might reduce translocation of GLUT4 to the plasma membrane. Other abnormalities include the accumulation of lipid 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. 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 mitogenic-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. The increased adipocyte mass leads to increased levels of circulating free fatty acids and other fat cell products (Chap. 77). For example, adipocytes secrete a number of biologic products (nonesterified free fatty acids, retinol-binding protein 4, leptin, TNF-α, resistin, and adiponectin). 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. For example, free fatty acids 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. In addition, inflammatory cells have been found infiltrating adipose tissue. Inhibition of inflammatory signaling pathways such as the nuclear factor κB (NF-κB) pathway appears to reduce insulin resistance and improve hyperglycemia in animal models.

**Impaired Insulin Secretion**

Insulin secretion and sensitivity are interrelated (Fig. 344-7). 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. The response to other nonglucose secretagogues, such as arginine, is preserved. Abnormalities in proinsulin processing is reflected by increased secretion of proinsulin in type 2 diabetes. Eventually, the insulin secretory defect progresses to a state of inadequate insulin secretion.

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 beta cell failure. Beta cell mass is decreased by approximately 50% in individuals with long-standing type 2 diabetes. Islet amyloid polypeptide or amylin is co-secreted by the beta cell and forms the amyloid fibrillar deposit 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 may also negatively impact 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. In addition, elevation of free fatty acid levels ("lipotoxicity") and dietary fat 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, though likely after the onset of insulin 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, leading to increased lipid [very low density lipoprotein (VLDL) and triglyceride] synthesis in hepatocytes. This lipid storage or steatosis in the liver may lead to nonalcoholic fatty liver disease (Chap. 309) and abnormal liver function tests. 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].

**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*, or *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 diabetes or IGT/IFG, and accelerated cardiovascular disease. This syndrome is discussed in Chap. 242.

A number of relatively rare forms of severe insulin resistance include features of type 2 DM or IGT (Table 344-1). 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 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 the type A insulin resistance syndrome have an undefined defect in the insulin-signaling pathway; individuals with the 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. 347). 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.

**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. 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. Studies in Finnish and Chinese populations noted similar efficacy of diet and exercise in preventing or delaying type 2 DM; α-glucosidase inhibitors, metformin, thiazolidinediones, and orlistat prevent or delay type 2 DM but are...
not approved for this purpose. Individuals with a strong family history of type 2 DM and individuals with IFG or IGT should be strongly encouraged to maintain 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 has suggested 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/m², family history of diabetes in first-degree relative, elevated triglycerides, reduced HDL, hypertension, or A1C >6.0%). Individuals with IFG, IGT, or an A1C of 5.7–6.4% should be monitored annually to determine if diagnostic criteria for diabetes are present.
GENETICALLY DEFINED, MONOGENIC FORMS OF DIABETES MELLITUS

Several monogenic forms of DM have been identified. Six different variants of MODY, caused by mutations in genes encoding islet-enriched transcription factors or glucokinase (Fig. 344-4; Table 344-1), are transmitted as autosomal dominant disorders. MODY 1, MODY 3, and MODY 5 are caused by mutations in the 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 or 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. Individuals with a HNF-1β mutation have progressive impairment of insulin secretion, hepatic insulin resistance, and require insulin treatment (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, stable hyperglycemia that does not respond to oral hypoglycemic agents. Glucokinase catalyzes the formation of glucose-6-phosphate from glucose, a reaction that is important for glucose sensing by the beta cells 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 the insulin promoter factor (IPF) 1, which is 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 may be caused by several genetic mutations and usually requires treatment with insulin. Mutations in the ATP-sensitive potassium channel subunits (Kir6.2 and ABCC8) and the insulin gene (interfere with proinsulin folding and processing) (Fig. 344-4) are the major causes of permanent neonatal diabetes. Although these activating mutations in the ATP-sensitive potassium channel subunits impair glucose-stimulated insulin secretion, these individuals may respond to sulfonylureas and be treated with these agents. These mutations are associated with a spectrum of neurologic dysfunction. Homozygous glucokinase mutations cause a severe form of neonatal diabetes.
ACUTE COMPLICATIONS OF DM

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are acute complications of diabetes. DKA was formerly considered a hallmark of type 1 DM, but also occurs in individuals who lack immunologic features of type 1 DM and who can sometimes subsequently be treated with oral glucose-lowering agents (these obese individuals with type 2 DM are often of Hispanic or African-American descent. The initial management of DKA is similar. 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 344-4. Both disorders are associated with potentially serious complications if not promptly diagnosed and treated.

<table>
<thead>
<tr>
<th>Table 344-4 Laboratory Values in Diabetic Ketoacidosis (DKA) and Hyperglycemic Hyperosmolar State (HHS) (Representative Ranges at Presentation)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DKA</strong></td>
</tr>
<tr>
<td>Glucose, a mmol/L (mg/dL)</td>
</tr>
<tr>
<td>Sodium, meq/L</td>
</tr>
<tr>
<td>Potassium a,b</td>
</tr>
<tr>
<td>Magnesium a</td>
</tr>
<tr>
<td>Chloride a</td>
</tr>
<tr>
<td>Phosphate a,b</td>
</tr>
<tr>
<td>Creatinine</td>
</tr>
<tr>
<td>Osmolality (mOsm/mL)</td>
</tr>
<tr>
<td>Plasma ketones a</td>
</tr>
<tr>
<td>Serum bicarbonate, a meq/L</td>
</tr>
</tbody>
</table>
**Diabetic Ketoacidosis**

**CLINICAL FEATURES**

The symptoms and physical signs of DKA are listed in **Table 344-5** 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 (infection, hypoxemia, etc.). 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. Tissue ischemia (heart, brain) can also be a precipitating factor. Omission of insulin because of an eating disorder may sometimes precipitate DKA.

<table>
<thead>
<tr>
<th>Table 344-5 Manifestations of Diabetic Ketoacidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Thirst/polyuria</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Shortness of breath</td>
</tr>
<tr>
<td><strong>Precipitating events</strong></td>
</tr>
<tr>
<td>Inadequate insulin administration</td>
</tr>
<tr>
<td>Infection (pneumonia/UTI/gastroenteritis/sepsis)</td>
</tr>
<tr>
<td>Infarction (cerebral, coronary, mesenteric, peripheral)</td>
</tr>
<tr>
<td>Drugs (cocaine)</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
</tbody>
</table>
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. Markers of inflammation (cytokines, C-reactive protein) are elevated in both DKA and HHS.

The combination of insulin deficiency and hyperglycemia reduces the hepatic level of fructose-2,6-bisphosphate, which alters the activity of phosphofructokinase and fructose-1,6-bisphosphatase. Glucagon excess decreases the activity of pyruvate kinase, whereas insulin deficiency increases the activity of phosphoenolpyruvate carboxykinase. These changes shift the handling of pyruvate toward glucose synthesis and away from glycolysis. The increased levels of glucagon and catecholamines in the face of low insulin levels promote glycogenolysis. Insulin deficiency also reduces levels of the GLUT4 glucose transporter, which impairs glucose uptake into skeletal muscle and fat and reduces intracellular glucose metabolism (Fig. 344-5).

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, increase lipolysis and the release of free fatty acids. Normally, these free fatty acids are converted to triglycerides or VLDL in the liver. However, in DKA, hyperglucagonemia alters hepatic metabolism to favor ketone body formation, through activation of the enzyme carnitine palmitoyltransferase I. This enzyme is crucial for regulating fatty acid transport into the mitochondria, where beta oxidation and conversion to ketone bodies occur. At physiologic pH, ketone bodies exist as ketoacids, which are neutralized by bicarbonate. As bicarbonate stores are depleted, metabolic acidosis ensues. Increased lactic acid production also contributes to the acidosis. The increased free fatty acids increase triglyceride and VLDL production. VLDL clearance is also reduced because the activity of insulin-sensitive lipoprotein lipase in muscle and fat is decreased. Hypertriglyceridemia may be severe enough to cause pancreatitis.

DKA is often precipitated by increased insulin requirements, as occurs during a concurrent illness (Table 344-5). Failure to augment insulin therapy often compounds the problem. 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. Patients using insulin infusion devices with short-acting insulin may develop DKA, since even a brief interruption in insulin delivery (e.g., mechanical malfunction) quickly leads to insulin deficiency.

LABORATORY ABNORMALITIES AND DIAGNOSIS

The timely diagnosis of DKA is crucial and allows for prompt initiation of therapy. DKA is characterized by hyperglycemia, ketosis, and metabolic acidosis (increased anion gap) along with a number of secondary metabolic derangements (Table 344-4). Occasionally, the serum glucose is only minimally elevated. Serum bicarbonate is frequently <10 mmol/L, and arterial pH 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. Total-body stores of sodium, chloride, phosphorus, and magnesium are reduced in DKA but are not accurately reflected by their levels in the serum because of dehydration and hyperglycemia. Elevated blood urea nitrogen (BUN) and
serum creatinine levels reflect intravascular volume depletion. Interference from acetoacetate may falsely elevate the serum creatinine measurement. 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 \([1.6 \text{ mmol/L (1.6 meq)}\) reduction in serum sodium for each \(5.6 \text{ mmol/L (100 mg/dL)}\) rise in the serum glucose]. A normal serum sodium in the setting of DKA indicates a more profound water deficit. In "conventional" units, the calculated serum osmolality \([2 \times (\text{serum sodium} + \text{serum potassium}) + \text{plasma glucose (mg/dL)/18} + \text{BUN/2.8}]\) is mildly to moderately elevated, though to a lesser degree than that found in HHS (see below).

In DKA, the ketone body, \(\beta\)-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 \(\beta\)-hydroxybutyrate are preferred since 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 since 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 \(>15 \text{ meq/L}\)) and other forms of increased anion-gap acidosis (Chap. 47).

**Tx**

**Treatment: Diabetic Ketoacidosis**

The management of DKA is outlined in **Table 344-6**. After initiating IV fluid replacement and insulin therapy, the agent or 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.

**Table 344-6 Management of Diabetic Ketoacidosis**

1. Confirm diagnosis (+plasma glucose, positive serum ketones, metabolic acidosis).
2. Admit to hospital; intensive-care setting may be necessary for frequent monitoring or if pH <7.00 or unconscious.
3. Assess:

   Serum electrolytes (K⁺, Na⁺, Mg²⁺, Cl⁻, bicarbonate, phosphate)

   Acid-base status—pH, HCO₃⁻, PCO₂, ß-hydroxybutyrate

   Renal function (creatinine, urine output)

4. Replace fluids: 2–3 L of 0.9% saline over first 1–3 h (15–20 mL/kg per hour); subsequently, 0.45% saline at 250–500 mL/h; change to 5% glucose and 0.45% saline at 150–250 mL/h when plasma glucose reaches 200 mg/dL (11.2 mmol/L).

5. Administer short-acting 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. If the initial serum potassium is >5.2 mmol/L (5.2 meq/L), do not supplement K⁺ until the potassium is corrected.

6. Assess patient: What precipitated the episode (noncompliance, infection, trauma, infarction, cocaine)? Initiate appropriate workup for precipitating event (cultures, CXR, ECG).

7. Measure capillary 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. See text about bicarbonate or phosphate supplementation.

10. Continue above until patient is stable, glucose goal is 8.3–13.9 mmol/L (150–250 mg/dL), and acidosis is resolved. Insulin infusion may be decreased to 0.05–0.1 units/kg per hour.

11. Administer long-acting insulin as soon as patient is eating. Allow for overlap in insulin infusion and SC insulin injection.

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


After the initial bolus of normal saline, 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 depending on the calculated volume deficit. The change to 0.45% saline helps to reduce the trend toward hyperchloremia later in the course of DKA. Alternatively, initial use of lactated Ringer's IV solution may reduce the hyperchloremia that commonly occurs with normal saline.

A bolus of IV (0.1 units/kg) short-acting insulin should be administered immediately (Table 344-6), and subsequent treatment should provide continuous and adequate levels of circulating insulin. IV administration is preferred (0.1 units/kg of regular insulin per hour), because it ensures rapid distribution and allows adjustment of the infusion rate as the patient responds to therapy. In mild episodes of DKA, short-acting insulin analogues can be used SC. IV 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 0.05–0.1 units/kg per hour). Long-acting insulin, in combination with SC short-acting insulin, should be administered as soon as the patient resumes eating, as this facilitates transition to an outpatient insulin regimen and reduces length of hospital stay. It is crucial to continue the insulin infusion 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.

Hyperglycemia usually improves at a rate of 4.2–5.6 mmol/L (75–100 mg/dL) per hour as a result of insulin-mediated glucose disposal, reduced hepatic glucose release, and rehydration. The latter 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 11.2 mmol/L (200 mg/dL), glucose should be added to the 0.45% saline infusion to maintain the plasma glucose in the 8.3–13.9 mmol/L (150–250 mg/dL) range, and the insulin infusion should be continued. 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. As ketoacidosis improves, β-hydroxybutyrate is converted to acetoacetate. Ketone body levels may appear to increase if measured by laboratory assays that use the nitroprusside reaction, which only detects acetoacetate and acetone. The improvement in acidosis and anion gap, a result of bicarbonate regeneration and decline in ketone bodies, is reflected by a rise in the serum bicarbonate level and the arterial pH. 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 <6.9), the ADA advises bicarbonate [50 mmol/L (meq/L) of sodium bicarbonate in 200 mL of sterile water with 10 meq/L KCl per hour for 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 < 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 gastrointestinal 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 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. During illness or when oral intake is compromised, patients should (1) frequently measure the capillary blood glucose; (2) measure urinary ketones when the serum glucose > 16.5 mmol/L (300 mg/dL); (3) drink fluids to maintain hydration; (4) continue or increase insulin; and (5) seek medical attention if dehydration, persistent vomiting, or uncontrolled hyperglycemia develop. Using these strategies, early DKA can be prevented or detected and treated appropriately on an outpatient basis.

**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 344-4. Most notable are the marked hyperglycemia [plasma glucose may be >55.5 mmol/L (1000 mg/dL)], hyperosmolality (>350 mosmol/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 344-6). 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 > 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, D5W). The calculated free water deficit (which averages 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 KPO4 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 units/kg followed by IV insulin at a constant infusion rate of 0.1 units/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 13.9–16.7 mmol/L (250–300 mg/dL), and the insulin infusion rate should be decreased to 0.05–0.1 units/kg per hour. The insulin infusion should be continued until the patient has resumed eating and can be transferred to a SC insulin regimen. The patient should be discharged from the hospital on insulin, though some patients can later switch to oral glucose-lowering agents.
The chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. Chronic complications can be divided into vascular and nonvascular complications (Table 344-7). The vascular complications of DM are further subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications [coronary heart disease (CHD), peripheral arterial disease (PAD), cerebrovascular disease]. Nonvascular complications include problems such as gastroparesis, infections, and skin changes. Long-standing diabetes may be associated with hearing loss. Whether type 2 DM in elderly individuals is associated with impaired mental function is not clear.

### Table 344-7 Chronic Complications of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Microvascular</th>
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<tbody>
<tr>
<td>Eye disease</td>
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<tr>
<td>Retinopathy (nonproliferative/proliferative)</td>
<td></td>
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<tr>
<td>Macular edema</td>
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<tr>
<td>Neuropathy</td>
<td></td>
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<tr>
<td>Sensory and motor (mono- and polyneuropathy)</td>
<td></td>
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<tr>
<td>Autonomic</td>
<td></td>
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<tr>
<td>Nephropathy</td>
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<tr>
<td>Macrovascular</td>
<td></td>
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<tr>
<td>Coronary heart disease</td>
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<tr>
<td>Peripheral arterial disease</td>
<td></td>
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<tr>
<td>Cerebrovascular disease</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
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<tr>
<td>Gastrointestinal (gastroparesis, diarrhea)</td>
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</tr>
<tr>
<td>Genitourinary (uropathy/sexual dysfunction)</td>
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<tr>
<td>Dermatologic</td>
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<tr>
<td>Infectious</td>
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<tr>
<td>Cataracts</td>
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<td>Glaucoma</td>
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<td>Periodontal disease</td>
<td></td>
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<tr>
<td>Hearing loss</td>
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</table>

The risk of chronic complications increases as a function of the duration and degree of hyperglycemia; they usually do not become apparent until the second decade of hyperglycemia. Since type 2 DM often has a long asymptomatic period of hyperglycemia, many individuals with type 2 DM have complications at the time of
diagnosis.

The microvascular complications of both type 1 and type 2 DM result from chronic hyperglycemia. Large, randomized clinical trials of individuals with type 1 or type 2 DM have conclusively demonstrated that a reduction in chronic hyperglycemia prevents or delays retinopathy, neuropathy, and nephropathy. Other incompletely defined factors may modulate the development of complications. For example, despite long-standing DM, some individuals never develop nephropathy or retinopathy. Many of these patients have glycemic control that is indistinguishable from those who develop microvascular complications, suggesting that there is a genetic susceptibility for developing particular complications.

Evidence implicating a causative role for chronic hyperglycemia in the development of macrovascular complications is less conclusive. However, coronary heart disease events and mortality rate are two to four times greater in patients with type 2 DM. These events correlate with fasting and postprandial plasma glucose levels as well as with the A1C. Other factors (dyslipidemia and hypertension) also play important roles in macrovascular complications.

**Mechanisms of Complications**

Although chronic hyperglycemia is an important etiologic factor leading to complications of DM, the mechanism(s) by which it leads to such diverse cellular and organ dysfunction is unknown. At least four prominent theories, which are not mutually exclusive, have been proposed to explain how hyperglycemia might lead to the chronic complications of DM. An emerging hypothesis is that hyperglycemia leads to epigenetic changes in the affected cells.

One theory is that increased intracellular glucose leads to the formation of advanced glycosylation end products (AGEs), which bind to a cell surface receptor, via the nonenzymatic glycosylation of intra- and extracellular proteins. Nonenzymatic glycosylation results from the interaction of glucose with amino groups on proteins. AGEs have been shown to cross-link proteins (e.g., collagen, extracellular matrix proteins), accelerate atherosclerosis, promote glomerular dysfunction, reduce nitric oxide synthesis, induce endothelial dysfunction, and alter extracellular matrix composition and structure. The serum level of AGEs correlates with the level of glycemia, and these products accumulate as the glomerular filtration rate (GFR) declines.

A second theory is based on the observation that hyperglycemia increases glucose metabolism via the sorbitol pathway. Intracellular glucose is predominantly metabolized by phosphorylation and subsequent glycolysis, but when increased, some glucose is converted to sorbitol by the enzyme aldose reductase. Increased sorbitol concentration alters redox potential, increases cellular osmolality, generates reactive oxygen species, and likely leads to other types of cellular dysfunction. However, testing of this theory in humans, using aldose reductase inhibitors, has not demonstrated significant beneficial effects on clinical endpoints of retinopathy, neuropathy, or nephropathy.

A third hypothesis proposes that hyperglycemia increases the formation of diacylglycerol leading to activation of protein kinase C (PKC). Among other actions, PKC alters the transcription of genes for fibronectin, type IV collagen, contractile proteins, and extracellular matrix proteins in endothelial cells and neurons. Inhibitors of PKC are being studied in clinical trials.

A fourth theory proposes that hyperglycemia increases the flux through the hexosamine pathway, which generates fructose-6-phosphate, a substrate for O-linked glycosylation and proteoglycan production. The hexosamine pathway may alter function by glycosylation of proteins such as endothelial nitric oxide synthase or by changes in gene expression of transforming growth factor β (TGF-β) or plasminogen activator inhibitor-1 (PAI-1).

Growth factors appear to play an important role in some DM-related complications, and their production is increased by most of these proposed pathways. Vascular endothelial growth factor A (VEGF-A) is increased
locally in diabetic proliferative retinopathy and decreases after laser photocoagulation. TGF-β is increased in diabetic nephropathy and stimulates basement membrane production of collagen and fibronectin by mesangial cells. Other growth factors, such as platelet-derived growth factor, epidermal growth factor, insulin-like growth factor 1, growth hormone, basic fibroblast growth factor, and even insulin, have been suggested to play a role in DM-related complications. A possible unifying mechanism is that hyperglycemia leads to increased production of reactive oxygen species or superoxide in the mitochondria; these compounds may activate all four of the pathways described above. 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.

Glycemic Control and Complications

The Diabetes Control and Complications Trial (DCCT) provided definitive proof that reduction in chronic hyperglycemia can prevent many of the early complications of type 1 DM. This large multicenter clinical trial randomized more than 1400 individuals with type 1 DM to either intensive or conventional diabetes management and prospectively evaluated the development of retinopathy, nephropathy, and neuropathy. Individuals in the intensive diabetes management group received multiple administrations of insulin each day along with extensive educational, psychological, and medical support. Individuals in the conventional diabetes management group received twice-daily insulin injections and quarterly nutritional, educational, and clinical evaluation. The goal in the former group was normoglycemia; the goal in the latter group was prevention of symptoms of diabetes. Individuals in the intensive diabetes management group achieved a substantially lower hemoglobin A1C (7.3%) than individuals in the conventional diabetes management group (9.1%).

The DCCT demonstrated that improvement of glycemic control reduced nonproliferative and proliferative retinopathy (47% reduction), microalbuminuria (39% reduction), clinical nephropathy (54% reduction), and neuropathy (60% reduction). Improved glycemic control also slowed the progression of early diabetic complications. There was a nonsignificant trend in reduction of macrovascular events during the trial (most individuals were young and had a low risk of cardiovascular disease). 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 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 or neurologic 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 long-term prognosis for type 1 diabetes continues to improve as shown by 30-year incidence data in the intensively treated group from the DCCT of retinopathy (21%), nephropathy (9%), and cardiovascular disease (9%). During this follow-up, fewer than 1% of the cohort had become blind, lost a limb to amputation, or required dialysis. The benefit of the improved glycemic control during the DCCT persisted even after the study concluded and glycemic control worsened. For example, individuals in the intensive diabetes management group for a mean of 6.5 years 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 17 years, even though their subsequent glycemic control was the same as those in the conventional diabetes management group from years 6.5–17 (discussed below).

The benefits of an improvement in glycemic control occurred over the entire range of A1C values (Fig. 344-8), suggesting that at any A1C level, an improvement in glycemic control is beneficial. The goal of therapy is to achieve an A1C level as close to normal as possible, without subjecting the patient to excessive risk of hypoglycemia.

Figure 344-8
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 A1C values. (Adapted from The Diabetes Control and Complications Trial Research Group: Diabetics 44:968, 1995.)

The United Kingdom Prospective Diabetes Study (UKPDS) studied the course of >5000 individuals with type 2 DM for >10 years. This study utilized 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 A1C of 7%, compared to a 7.9% A1C in the standard treatment group. The UKPDS demonstrated that each percentage point reduction in A1C 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 did not conclusively reduce (nor worsen) cardiovascular mortality rate during the period of the trial, but was associated with improvement with lipoprotein risk profiles, such as reduced triglycerides and increased HDL.

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 end-points, retinopathy, and heart failure (risk reductions between 32 and 56%).

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 findings of the DCCT, UKPDS, and Kumamoto study strongly support the idea that chronic hyperglycemia plays a causative role in the pathogenesis of diabetic microvascular complications. These landmark studies prove the value of metabolic control and emphasize the importance of (1) intensive glycemic control in all
forms of DM and (2) early diagnosis and strict blood pressure control in type 2 DM. Optimal targets for glycemic control and blood pressure are not entirely clear (see below).

**Ophthalmologic Complications of Diabetes Mellitus**

DM is the leading cause of blindness between the ages of 20 and 74 in the United States. The gravity of this problem is highlighted by the finding that individuals with DM are 25 times more likely to become legally blind than individuals without DM. Blindness is primarily the result of progressive diabetic retinopathy and clinically significant macular edema. 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 the disease and is marked by retinal vascular microaneurysms, blot hemorrhages, and cotton-wool spots (Fig. 344-9). Mild nonproliferative retinopathy progresses 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 lead to retinal ischemia.

**Figure 344-9**

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.

The appearance of neovascularization in response to retinal hypoxemia is the hallmark of proliferative diabetic retinopathy (Fig. 344-9). 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 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 when only nonproliferative retinopathy is present. Fluorescein angiography is 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 is also a risk factor. Nonproliferative retinopathy is found in many individuals who have had DM for >20 years (25% incidence with 5 years, and 80% incidence with 15 years of type 1 DM). Although there is genetic susceptibility for retinopathy, it confers less influence than either the duration of DM or the degree of glycemic control.

**Tx**

**Treatment: Diabetic Retinopathy**

The most effective therapy for diabetic retinopathy is prevention. Intensive glycemic and blood pressure control will delay the development or 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 are candidates for prophylactic photocoagulation when initiating intensive therapy. Once advanced retinopathy is present, improved glycemic control imparts less benefit, though adequate ophthalmologic care can prevent most blindness.

Regular, comprehensive eye examinations are essential for all individuals with DM. 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 an ophthalmologist for optimal care of these disorders. Laser photocoagulation is very successful in preserving vision. Proliferative retinopathy is usually treated with panretinal laser photocoagulation, whereas macular edema is treated with focal laser photocoagulation. Although exercise has not been conclusively shown to worsen proliferative diabetic retinopathy, most ophthalmologists advise individuals with advanced diabetic eye disease to limit physical activities associated with repeated Valsalva maneuvers. Aspirin therapy (650 mg/d) does not appear to influence the natural history of diabetic retinopathy.

**Renal Complications of Diabetes Mellitus**

Diabetic nephropathy is the leading cause of ESRD in the United States and a leading cause of DM-related morbidity and mortality. Both microalbuminuria and macroalbuminuria in individuals with DM are associated with increased risk of cardiovascular disease. Individuals with diabetic nephropathy commonly have diabetic retinopathy.

Like other microvascular complications, the pathogenesis of diabetic nephropathy is related to chronic hyperglycemia. The mechanisms by which chronic hyperglycemia leads to ESRD, though 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 receptors. Smoking accelerates the decline in renal function. Because only 20–40% of patients with diabetes develop diabetic nephropathy, additional susceptibility factors remain unidentified. One known risk factor is a family history of diabetic nephropathy.

The natural history of diabetic nephropathy is characterized by a fairly predictable sequence of events that was initially defined for individuals with type 1 DM but appears to be similar in type 2 DM (Fig. 344-10). Glomerular hyperperfusion and renal hypertrophy occur in the first years after the onset of DM and are associated with an increase of the 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, ~40% of individuals begin to excrete small amounts of albumin in the urine. Microalbuminuria is defined as 30–299 mg/d in a 24-h collection or 30–299 μg/mg creatinine in a spot collection.
Although the appearance of microalbuminuria in type 1 DM is an important risk factor for progression to macroalbuminuria (>300 mg/d or > 300 μg/mg creatinine), only ~50% of individuals progress to macroalbuminuria over the next 10 years. In some individuals with type 1 diabetes and microalbuminuria of short duration, the microalbuminuria regresses. Microalbuminuria is a risk factor for cardiovascular disease. Once macroalbuminuria is present, there is a steady decline in GFR, and ~50% of individuals reach ESRD in 7–10 years. Once macroalbuminuria develops, blood pressure rises slightly and the pathologic changes are likely irreversible.

**Figure 344-10**

Time course of development of diabetic nephropathy. The relationship of time from onset of diabetes, the glomerular filtration rate (GFR), and the serum creatinine are shown. (Adapted from RA DeFranzo, in Therapy for Diabetes Mellitus and Related Disorders, 3rd ed. American Diabetes Association, Alexandria, VA, 1998.)

The nephropathy that develops in type 2 DM differs from that of type 1 DM in the following respects: (1) microalbuminuria or macroalbuminuria may be present when type 2 DM is diagnosed, reflecting its long asymptomatic period; (2) hypertension more commonly accompanies microalbuminuria or macroalbuminuria in type 2 DM; and (3) microalbuminuria may be less predictive of diabetic nephropathy and progression to macroalbuminuria in type 2 DM. 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. Diabetic nephropathy and ESRD secondary to DM develop more commonly in African Americans, Native Americans, and Hispanic individuals than in Caucasians with 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, which may be exacerbated by medications [especially angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)]. 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.

**Tx**

**Treatment: Diabetic Nephropathy**

The optimal therapy for diabetic nephropathy is prevention by control of glycemia. As part of comprehensive diabetes care, microalbuminuria should be detected at an early stage when effective therapies can be instituted. The recommended strategy for detecting microalbuminuria is outlined in Fig. 344-11. Since some individuals with type 1 or type 2 DM have a decline in GFR in the absence of micro- or macroalbuminuria, annual measurement of the serum creatinine to estimate GFR should also be performed. Interventions effective
in slowing progression from microalbuminuria to macroalbuminuria include (1) normalization of glycemia, (2) strict blood pressure control, and (3) administration of ACE inhibitors or ARBs. Dyslipidemia should also be treated.

**Figure 344-11**

![Diagram](image)


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**Screening for microalbuminuria** should be performed in patients with type 1 diabetes for ≥5 years, in patients with type 2 diabetes, and during pregnancy. Non-diabetes-related conditions that might increase microalbuminuria are urinary tract infection, hematuria, heart failure, febrile illness, severe hyperglycemia, severe hypertension, and vigorous exercise. *(Adapted from RA DeFronzo, in Therapy for Diabetes Mellitus and Related Disorders, 3rd ed. American Diabetes Association, Alexandria, VA, 1998.)*

Improved glycemic control reduces the rate at which microalbuminuria appears and progresses in type 1 and type 2 DM. However, once macroalbuminuria exists, it is unclear whether improved glycemic control will slow progression of renal disease. During the later phase of declining renal function, insulin requirements may fall as the kidney is a site of insulin degradation. Furthermore, many glucose-lowering medications (sulfonylureas and metformin) are contraindicated in advanced renal insufficiency.

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 <130/80 mmHg in diabetic individuals.

Either ACE inhibitors or ARBs should be used to reduce the progression from microalbuminuria to macroalbuminuria and the associated decline in GFR that accompanies macroalbuminuria in individuals with type 1 or type 2 DM (see "Hypertension," below). Although direct comparisons of ACE inhibitors and ARBs are lacking, most experts believe that the two classes of drugs are equivalent in the patient with diabetes. ARBs can be used as an alternative in patients who develop ACE inhibitor–associated cough or angioedema. After 2–3 months of therapy in patients with microalbuminuria, the drug dose is increased until either the
microalbuminuria disappears or the maximum dose is reached. If use of either ACE inhibitors or ARBs is not possible or the blood pressure is not controlled, then calcium channel blockers (non-dihydropyridine class), beta blockers, or diuretics should be used. However, their efficacy in slowing the fall in the GFR is not proven. Blood pressure control with any agent is extremely important, but a drug-specific benefit in diabetic nephropathy, independent of blood pressure control, has been shown only for ACE inhibitors and ARBs in patients with DM.

The ADA suggests modest restriction of protein intake in diabetic individuals with microalbuminuria (0.8–1.0 g/kg per day) or macroalbuminuria (<0.8 g/kg per day).

Nephrology consultation should be considered when the estimated GFR <60 mL/min per 1.743 m². Once macroalbuminuria ensues, the likelihood of ESRD is very high. As compared to 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. Survival after the onset of ESRD is shorter in the diabetic population compared to nondiabetics with similar clinical features. Atherosclerosis is the leading cause of death in diabetic individuals on dialysis, and hyperlipidemia should be treated aggressively. Renal transplantation from a living related donor is the preferred therapy but requires chronic immunosuppression. Combined pancreas-kidney transplant offers the promise of normoglycemia and freedom from dialysis.

Neuropathy and Diabetes Mellitus

Diabetic neuropathy occurs in ~50% of individuals with long-standing type 1 and type 2 DM. It may manifest as polyneuropathy, mononeuropathy, and/or autonomic neuropathy. As with other complications of DM, the development of neuropathy correlates with the duration of diabetes and glycemic control. Additional risk factors are BMI (the greater the BMI, the greater the risk of neuropathy) and smoking. The presence of cardiovascular disease, 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. 384).

POLYNEUROPATHY/MONONEUROPATHY

The most common form of diabetic neuropathy is distal symmetric polyneuropathy. It most frequently presents with distal sensory loss, but up to 50% of patients do not have symptoms of neuropathy. Hyperesthesia, paresthesia, and dysesthesia also may occur. Any combination of these symptoms may develop as neuropathy progresses. Symptoms may include a sensation of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally. Neuropathic pain develops in some of these individuals, occasionally preceded by improvement in their glycemic control. 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 have been described. As diabetic neuropathy progresses, the pain subsides and eventually disappears, but a sensory deficit in the lower extremities persists. Physical examination reveals sensory loss, loss of ankle reflexes, and abnormal position sense.

Diabetic 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.

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. A vascular etiology has been suggested, but the pathogenesis is unknown. 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 IV, VI, or VII (Bell’s palsy) are affected. Peripheral mononeuropathies or simultaneous involvement of more than one nerve (mononeuropathy multiplex) may also occur.

**AUTONOMIC NEUROPATHY**

Individuals with long-standing type 1 or 2 DM may develop signs of autonomic dysfunction involving the cholinergic, noradrenergic, and peptidergic (peptides such as pancreatic polypeptide, substance P, etc.) systems. DM-related autonomic neuropathy can involve multiple systems, including the cardiovascular, gastrointestinal, genitourinary, sudomotor, and metabolic systems. Autonomic neuropathies affecting the cardiovascular system cause a resting tachycardia and orthostatic hypotension. Reports of sudden death have also been attributed to autonomic neuropathy. 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. Autonomic neuropathy may reduce counterregulatory hormone release (especially catecholamines), leading to an inability to sense hypoglycemia appropriately (hypoglycemia unawareness; Chap. 345), thereby subjecting the patient to the risk of severe hypoglycemia and complicating efforts to improve glycemic control.

**Treatment: Diabetic Neuropathy**

Treatment of diabetic neuropathy is less than satisfactory. Improved glycemic control should be aggressively pursued and will improve nerve conduction velocity, but symptoms of diabetic neuropathy may not necessarily improve. Efforts to improve glycemic control may be confounded by autonomic neuropathy and hypoglycemia unawareness. Risk factors for neuropathy such as hypertension and hypertriglyceridemia should be treated. Avoidance of neurotoxins (alcohol) and smoking, supplementation with vitamins for possible deficiencies (B<sub>12</sub>, folate; Chap. 74), and symptomatic treatment are the mainstays of therapy. Loss of sensation in the foot places the patient at risk for ulceration and its sequelae; consequently, prevention of such problems is of paramount importance. Patients with symptoms or signs of neuropathy (see "Physical Examination," below) 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 but may respond to antidepressants (tricyclic antidepressants such as amitriptyline, desipramine, nortriptyline, imipramine or selective serotonin-norepinephrine reuptake inhibitors such as duloxetine) or anticonvulsants (gabapentin, pregabalin, carbamazepine, lamotrigine). Two agents, duloxetine and pregabalin, have been approved by the U.S. Food and Drug Administration (FDA) for pain associated with diabetic neuropathy. However, pending further study, most recommend beginning with other agents such as a tricyclic antidepressant and switching if there is no response or if side effects develop. Referral to a pain management center may be necessary. Since the pain of acute diabetic neuropathy may resolve over time, medications may be discontinued as progressive neuronal damage from DM occurs.

Therapy of orthostatic hypotension secondary to autonomic neuropathy is also challenging. A variety of agents have limited success (fludrocortisone, midodrine, clonidine, octreotide, and yohimbine) but each has significant side effects. Nonpharmacologic maneuvers (adequate salt intake, avoidance of dehydration and diuretics, and lower extremity support hose) may offer some benefit.

**Gastrointestinal/Genitourinary Dysfunction**

Long-standing type 1 and 2 DM may affect the motility and function of gastrointestinal (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 under development. Though 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 sprue because of its increased frequency. Esophageal dysfunction in long-standing DM may occur but is usually asymptomatic.

Diabetic autonomic neuropathy may lead to genitourinary dysfunction including cystopathy, erectile dysfunction, 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. Diagnostic evaluation includes cystometry and urodynamic studies.

Erectile dysfunction and retrograde ejaculation are very common in DM and may be one of the earliest signs of diabetic neuropathy (Chap. 48). 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. Improved glycemic control should be a primary goal, as some aspects (neuropathy, gastric function) may improve. Smaller, more frequent meals that are easier to digest (liquid) and low in fat and fiber may minimize symptoms of gastroparesis. Agents with some efficacy include dopamine antagonists metoclopramide, 5–10 mg, and domperidone, 10–20 mg, before each meal. Erythromycin interacts with the motilin receptor and may promote gastric emptying. Diabetic diarrhea in the absence of bacterial overgrowth is treated symptomatically with loperamide and may respond to octreotide (50–75 μg three times daily, SC). Treatment of bacterial overgrowth with antibiotics is sometimes useful (Chap. 294).

Diabetic cystopathy should be treated with timed voiding or self-catheterization, possibly with the addition of bethanechol. 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. 48). Sexual dysfunction in women may be improved with use of vaginal lubricants, treatment of vaginal infections, and systemic or local estrogen replacement.

Cardiovascular Morbidity and Mortality

Cardiovascular disease is increased in individuals with type 1 or type 2 DM. The Framingham Heart Study revealed a marked increase in PAD, CHF, CHD, MI, and sudden death (risk increase from one- to fivefold) in DM. The American Heart Association has designated DM as a "CHD risk equivalent." Type 2 diabetes patients without a prior MI have a similar risk for coronary artery-related events as nondiabetic individuals who have had a prior MI. Because of the extremely high prevalence of underlying cardiovascular disease 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 suggestive of cardiac ischemia or peripheral or carotid arterial disease. The screening of asymptomatic individuals with diabetes for CHD is controversial, and recent studies have not shown a clinical benefit. The absence of chest pain ("silent ischemia") is common in
individuals with diabetes, and a thorough cardiac evaluation should be considered in individuals undergoing major surgical procedures. The prognosis for individuals with diabetes who have CHD or MI is worse than for nondiabetics. CHD is more likely to involve multiple vessels in individuals with DM.

The increase in cardiovascular morbidity and mortality rates appears to relate to the synergism of hyperglycemia with other cardiovascular risk factors. For example, after controlling for all known cardiovascular risk factors, type 2 DM increases the cardiovascular death rate twofold in men and fourfold in women. Risk factors for macrovascular disease in diabetic individuals include dyslipidemia, hypertension, obesity, reduced physical activity, and cigarette smoking. Additional risk factors more prevalent in the diabetic population include microalbuminuria, macroalbuminuria, an elevation of serum creatinine, and abnormal platelet function. Insulin resistance, as reflected by elevated serum insulin levels, is associated with an increased risk of cardiovascular complications in individuals with and without DM. Individuals with insulin resistance and type 2 DM have elevated levels of plasminogen activator inhibitors (especially PAI-1) and fibrinogen, which enhances the coagulation process and impairs fibrinolysis, thus favoring the development of thrombosis. Diabetes is also associated with endothelial, vascular smooth-muscle, and platelet dysfunction.

Improved glycemic control started soon after the diagnosis of diabetes reduces cardiovascular complications in DM, but the glycemic goal for individuals with long-standing diabetes remains unclear. In both the DCCT (type 1 diabetes) and the UKPDS (type 2 diabetes), cardiovascular events were not reduced by intensive treatment during the trial but were reduced at follow-up 10–17 years later (this effect has been termed legacy effect or metabolic memory). During the DCCT, an improvement in the lipid profile of individuals in the intensive group (lower total and LDL cholesterol, lower triglycerides) during intensive diabetes management was noted. Trials to examine whether very aggressive glycemic targets (A1C near 6%) reduce cardiovascular events in type 2 diabetes did not show a survival benefit of reducing the A1C below 7% (and in one trial, the outcome was worse). Current recommendations do not suggest more aggressive glucose lowering in this patient population. The possibility of atherogenic potential of insulin is suggested by the data in nondiabetic individuals showing higher serum insulin levels (indicative of insulin resistance) in association with greater risk of cardiovascular morbidity and mortality. However, treatment with insulin and the sulfonylureas did not appear to increase the risk of cardiovascular disease in individuals with type 2 DM, refuting prior claims about the atherogenic potential of these agents.

In addition to CHD, cerebrovascular disease is increased in individuals with DM (threelfold increase in stroke). Individuals with DM have an increased incidence of CHF. The etiology of this abnormality is probably multifactorial and includes factors such as myocardial ischemia from atherosclerosis, hypertension, and myocardial cell dysfunction secondary to chronic hyperglycemia.

**Treatment: Cardiovascular Disease**

In general, the treatment of coronary disease is not different in the diabetic individual (Chap. 243). Revascularization procedures for CHD, including percutaneous coronary interventions (PCI) and coronary artery bypass grafting (CABG), may be less efficacious in the diabetic individual. Initial success rates of PCI in diabetic individuals are similar to those in the nondiabetic population, but diabetic patients have higher rates of restenosis and lower long-term patency and survival rates in older studies. More recently, the use of drug-eluting stents and a GPIIb/IIIa platelet inhibitor has improved the outcomes in diabetic patients, and whether there is a difference in efficacy of PCI in diabetic individuals is not clear. Although CABG may be preferred over PCI in diabetic individuals with multivessel coronary artery disease or recent Q-wave MI, PCI is preferred in patients with single-vessel coronary artery disease or two-vessel disease (no involvement of left anterior descending).

The ADA has emphasized the importance of glycemic control and aggressive cardiovascular risk modification in
all individuals with DM (see below). Past trepidation about using beta blockers in individuals who have diabetes should not prevent use of these agents since they clearly benefit diabetic patients after MI. ACE inhibitors (or ARBs) may also be particularly beneficial and should be considered in individuals with type 2 DM and other risk factors (smoking, dyslipidemia, history of cardiovascular disease, microalbuminuria). Patients with atypical chest pain or an abnormal resting ECG should be considered for screening for CHD.

Antiplatelet therapy reduces cardiovascular events in individuals with DM who have CHD. Current recommendations by the ADA include the use of aspirin for secondary prevention of coronary events and the consideration of aspirin use in diabetic individuals with an increased cardiovascular risk (based on risk stratification using risk factors such as hypertension, smoking, family history, albuminuria, or dyslipidemia). Data demonstrating efficacy of aspirin in primary prevention of coronary events in individuals with DM and a low risk for CHD are lacking. The aspirin dose (75–162 mg) is the same as that in nondiabetic individuals. Aspirin therapy does not have detrimental effects on renal function or hypertension, nor does it influence the course of diabetic retinopathy.

CARDIOVASCULAR RISK FACTORS

Dyslipidemia

Individuals with DM may have several forms of dyslipidemia (Chap. 356). Because of the additive cardiovascular risk of hyperglycemia and hyperlipidemia, lipid abnormalities should be assessed aggressively and treated as part of comprehensive diabetes care. 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. Intervventional studies have shown that the beneficial effects of LDL reduction are similar in the diabetic and nondiabetic populations. Large prospective trials of primary and secondary intervention for CHD have included some individuals with type 2 DM, and subset analyses have consistently found that reductions in LDL reduce cardiovascular events and morbidity in individuals with DM. No prospective studies have addressed similar questions in individuals with type 1 DM. Since the frequency of cardiovascular disease is low in children and young adults with diabetes, assessment of CV risk should be incorporated into the guidelines discussed below.

Based on the guidelines provided by the ADA and the American Heart Association, priorities in the treatment of dyslipidemia are as follows: (1) lower the LDL cholesterol, (2) raise the HDL cholesterol, and (3) decrease the triglycerides. A treatment strategy depends on the pattern of lipoprotein abnormalities. Initial therapy for all forms of dyslipidemia should include dietary changes, as well as the same lifestyle modifications recommended in the nondiabetic population (smoking cessation, blood pressure control, weight loss, increased physical activity). The dietary recommendations for individuals with DM are similar to those advocated by the National Cholesterol Education Program (Chap. 356) and include increased monounsaturated fat and carbohydrates and reduced saturated fats and cholesterol. Though viewed as important, the response to dietary alterations is often modest (<10% reduction in the LDL). Improvement in glycemic control will lower triglycerides and have a modest beneficial effect by raising HDL. HMG-CoA reductase inhibitors are the agents of choice for lowering the LDL. According to guidelines of the ADA and the American Heart Association, the target lipid values in diabetic individuals (age >40 years) without cardiovascular disease should be as follows: LDL < 2.6 mmol/L (100 mg/dL); HDL >1 mmol/L (40 mg/dL) in men and >1.3 mmol/L (50 mg/dL) in women; and triglycerides <1.7 mmol/L (150 mg/dL). In patients >40 years, the ADA recommends addition of a statin, regardless of the LDL level in patients with CHD and those without CHD, but who have CHD risk factors.

If the patient is known to have CHD, the ADA recommends an LDL goal of <1.8 mmol/L (70 mg/dL) as an
"option" [in keeping with evidence that such a goal is beneficial in nondiabetic individuals with CHD (Chap. 356)]. Older studies with fibrates indicated efficacy, but recent trials have not shown a benefit of this class of agents. Combination therapy with an HMG-CoA reductase inhibitor and a fibrate or another lipid-lowering agent (ezetimibe, niacin) may be considered to reach LDL goals, but statin/fibrate combinations increase the possibility of side effects such as myositis. Nicotinic acid effectively raises HDL and can be used in patients with diabetes, but high doses (>2 g/d) may worsen glycemic control and increase insulin resistance. Bile acid–binding resins should not be used if hypertriglyceridemia is present.

**Hypertension**

Hypertension can accelerate other complications of DM, particularly cardiovascular disease and nephropathy. In targeting a goal of BP <130/80 mmHg, therapy should first emphasize life-style modifications such as weight loss, exercise, stress management, and sodium restriction. 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. Subsequently, agents that reduce cardiovascular risk (beta blockers, thiazide diuretics, and calcium channel blockers) should be incorporated into the regimen. While ACE inhibitors and ARBs are likely equivalent in most patients with diabetes and renal disease, the ADA notes (1) in patients with type 1 diabetes, hypertension, and micro- or macroalbuminuria, an ACE inhibitor slowed progression of nephropathy; (2) an ACE inhibitor or an ARB slowed the progression to macroalbuminuria in patients with type 2 diabetes, hypertension, and microalbuminuria; and (3) ARB slowed the decline in GFR in patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency. Additional points of emphasis include the following:

1. ACE inhibitors are either glucose- and lipid-neutral or glucose- and lipid-beneficial and thus positively impact the cardiovascular risk profile. Calcium channel blockers, central adrenergic antagonists, and vasodilators are lipid- and glucose-neutral.
2. Beta blockers and thiazide diuretics can increase insulin resistance and negatively impact the lipid profile; beta blockers may slightly increase the risk of developing type 2 DM. Beta blockers are safe in patients with diabetes and reduce cardiovascular events.
3. Sympathetic inhibitors and α-adrenergic blockers may worsen orthostatic hypotension in the diabetic individual with autonomic neuropathy.
4. Equivalent reduction in blood pressure by different classes of agents may not translate into equivalent protection from cardiovascular and renal endpoints. Thiazides, beta blockers, ACE inhibitors, and ARBs positively impact cardiovascular endpoints (MI or stroke).
5. 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 (hammertoe, 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.

Approximately 15% of individuals with type 2 DM develop a foot ulcer (great toe or MTP areas are most common), and a significant subset will ultimately undergo amputation (14–24% risk with that ulcer or subsequent ulceration). Risk factors for foot ulcers or amputation include: male sex, diabetes >10 years’ duration, peripheral neuropathy, abnormal structure of foot (bony abnormalities, callus, thickened nails), peripheral arterial disease, smoking, history of previous ulcer or amputation, and poor glycemic control. Large calluses are often precursors to or overlie ulcerations.

**Tx**

**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 foot examination performed on all patients with DM (see "Ongoing Aspects of Comprehensive Diabetes Care," below). 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. Patients at high risk for ulceration or amputation may benefit from evaluation by a foot care specialist. 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 is also frequent and should be treated with antibiotics that provide broad-spectrum coverage, including anaerobes (see below).

An infected ulcer is a clinical diagnosis, since superficial culture of any ulceration will likely find multiple possible bacterial species. The infection surrounding the foot ulcer is often the result of multiple organisms (gram-positive and -negative organisms and anaerobes), and gas gangrene may develop in the absence of clostridial infection. Cultures taken from the surface of the ulcer are not helpful; a culture from the debrided ulcer base or from purulent drainage or aspiration of the wound is the most helpful. Wound depth should be determined by inspection and probing with a blunt-tipped sterile instrument. Plain radiographs of the foot should be performed to assess the possibility of osteomyelitis in chronic ulcers that have not responded to therapy. Nuclear medicine bone scans may be helpful, but overlying subcutaneous infection is often difficult to distinguish from osteomyelitis. Indium-labeled white cell studies are more useful in determining if the infection involves bony structures or only soft tissue, but they are technically demanding. MRI of the foot may be the most specific modality, although distinguishing bony destruction due to osteomyelitis from destruction secondary to Charcot arthropathy is difficult. If surgical debridement is necessary, bone biopsy and culture may provide the answer.

Osteomyelitis is best treated by a combination of prolonged antibiotics (IV, then oral) and possibly debridement of infected bone. The possible contribution of vascular insufficiency should be considered in all patients. Noninvasive blood-flow studies are often unreliable in DM, and angiography may be required, recognizing the risk of contrast-induced nephrotoxicity. Peripheral arterial bypass procedures are often effective in promoting wound healing and in decreasing the need for amputation of the ischemic limb.
A growing number of possible treatments for diabetic foot ulcers exist, but they have yet to demonstrate clear efficacy in prospective, controlled trials. A consensus statement from the ADA identified six interventions with demonstrated efficacy in diabetic foot wounds: (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 clear efficacy of other modalities for wound cleaning (enzymes, soaking, whirlpools) is lacking. Dressings such as hydrocolloid dressings promote wound healing by creating a moist environment 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 (cephalosporin, clindamycin, amoxicillin/clavulanate, and fluoroquinolones), surgical debridement of necrotic tissue, local wound care (avoidance of weight bearing over the ulcer), and close surveillance for progression of infection. More severe ulcers may require IV antibiotics as well as bed rest and local wound care. Urgent surgical debridement may be required. Strict control of glycemia should be a goal (see below). IV antibiotics should provide broad-spectrum coverage directed toward \textit{Staphylococcus aureus}, streptococci, gram-negative aerobes, and anaerobic bacteria. Initial antimicrobial regimens include ertapenem, piperacillin/tazobactam, cefotetan, ampicillin/sulbactam, linezolid, or the combination of clindamycin and a fluoroquinolone. Severe infections, or infections that do not improve after 48 h of antibiotic therapy, require expansion of antimicrobial therapy to treat methicillin-resistant \textit{S. aureus} (e.g., vancomycin) and \textit{Pseudomonas aeruginosa}. 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.

New information about wound biology has led to a number of new technologies (e.g., living skin equivalents and growth factors) that may prove useful, especially in neuropathic ulcers. Hyperbaric oxygen has been used, but rigorous proof of efficacy is lacking. Negative wound pressure has been shown to accelerate wound healing of plantar wounds.

\section*{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 (\textit{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 gall bladder and urinary tract, and "malignant" or invasive otitis externa. Invasive otitis externa is usually secondary to \textit{P. 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 HHS.

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, \textit{S. aureus}, and \textit{Mycobacterium tuberculosis} are more frequent pathogens. Urinary tract infections (either lower tract or pyelonephritis) are the result of common bacterial agents such as \textit{Escherichia coli}, though several yeast species (\textit{Candida} and \textit{Torulopsis glabrata}) are commonly observed. Complications of urinary tract infections include emphysematous pyelonephritis and emphysematous cystitis. Bacteriuria occurs frequently in individuals with diabetic
cystopathy. Susceptibility to furunculosis, superficial candidal infections, and vulvovaginitis are increased. Poor glycemic control is a common denominator in individuals with these infections. Diabetic individuals have an increased rate of colonization of *S. aureus* in the skinfolds and nares. Diabetic patients also have a greater risk of postoperative wound infections. Strict glycemic control reduces postoperative infections in diabetic individuals undergoing CABG and should be the goal in all diabetic patients with an infection.

**Dermatologic Manifestations**

The most common skin manifestations of DM are protracted wound healing and skin ulcerations. Diabetic dermopathy, sometimes termed *pigmented pretibial papules*, or "diabetic skin spots," begins as an erythematous area and 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 bullous diabeticorum (shallow ulcerations or erosions in the pretibial region), are also seen. *Necrobiosis lipoidica diabeticorum* is a rare disorder of DM that predominantly affects young women with type 1 DM, neuropathy, and retinopathy. It 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 may be painful. Vitiligo occurs at increased frequency in individuals with type 1 diabetes. *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) 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. Xerosis and pruritus are common and are relieved by skin moisturizers.

**Approach to the Patient: Diabetes Mellitus**

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 complications begin to appear during the second decade of hyperglycemia. 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 should screen for the chronic complications and conditions associated with DM.

**HISTORY**

A complete medical history should be obtained with special emphasis on DM-relevant aspects such as weight, family history of DM and its complications, risk factors for cardiovascular disease, exercise, smoking, 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 the hyperglycemia is controlled.

In a patient with established DM, the initial assessment should also include special emphasis on prior diabetes care, including the type of therapy, prior A1C levels, self-monitoring blood glucose results, frequency of hypoglycemia, presence of DM-specific complications, and assessment of the patient's knowledge about diabetes, exercise, and nutrition. The chronic 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 (see above). In addition, the presence of DM-related comorbidities should be sought (cardiovascular disease, hypertension, dyslipidemia).

**PHYSICAL EXAMINATION**
In addition to a complete physical examination, special attention should be given to DM-relevant aspects such as weight or BMI, retinal examination, orthostatic blood pressure, foot examination, peripheral pulses, and insulin injection sites. Blood pressure >130/80 mmHg is considered hypertension in individuals with diabetes. Careful examination of the lower extremities should seek evidence of peripheral arterial disease (pedal pulses), peripheral neuropathy, calluses, superficial fungal infections, nail disease, ankle reflexes, and foot deformities (such as hammertoes or claw toes and Charcot foot) in order to identify sites of potential skin ulceration. 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, testing for ankle reflexes, and vibration perception threshold (using a biothesiometer) are used to detect moderately advanced diabetic neuropathy. Since periodontal disease is more frequent in DM, the teeth and gums should also be examined.

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 tend to have the following characteristics: (1) onset of disease prior to age 30 years; (2) lean body habitus; (3) requirement of insulin as the initial therapy; (4) propensity to develop ketoacidosis; and (5) an increased risk 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) develop diabetes after the age of 30 years; (2) are usually obese (80% are obese, but elderly individuals may be lean); (3) may not require insulin therapy initially; and (4) may have associated conditions such as insulin resistance, hypertension, cardiovascular disease, dyslipidemia, or PCOS. 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 DKA 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 (ICA, GAD autoantibodies) suggestive of type 1 DM (termed latent autoimmune diabetes of the adult). Such individuals are more likely to be <50 years of age, have a normal BMI, and have a personal or family history of other autoimmune disease. They are much more likely to require insulin treatment within 5 years. Monogenic forms of diabetes (discussed above) should be considered in those with diabetes onset <30 years of age, an autosomal pattern of diabetes inheritance, and the lack of nearly complete insulin deficiency. Despite recent advances in the understanding of the pathogenesis of diabetes, it 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, and other endocrine disorders, should be classified accordingly (Table 344-1).

LABORATORY ASSESSMENT

The laboratory assessment should first determine whether the patient meets the diagnostic criteria for DM (Table 344-2) and then assess the degree of glycemic control (A1C, discussed below). In addition to the standard laboratory evaluation, the patient should be screened for DM-associated conditions (e.g., microalbuminuria, dyslipidemia, thyroid dysfunction). Individuals at high risk for cardiovascular disease should be screened for asymptomatic CHD by appropriate cardiac stress testing, when indicated.

The classification of the type of DM may be facilitated by laboratory assessments. Serum insulin or C-peptide measurements do not always distinguish type 1 from type 2 DM, but a low C-peptide level confirms a patient’s need for insulin. Many individuals with new-onset 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.
LONG-TERM TREATMENT

Overall Principles

The goals of therapy for type 1 or type 2 DM are to (1) eliminate symptoms related to hyperglycemia, (2) prevent macrovascular complications of DM, and (3) allow the patient to achieve as normal a lifestyle as possible. To reach these goals, the level of glycemic control for each patient, provide the patient with the educational and pharmacologic resources necessary to reach the second and third goals. Symptoms of diabetes usually resolve when the plasma glucose is <11.1 mmol/L (<200 mg/dL) achieving the second and third goals. The treatment goals for patients with diabetes are summarized in Table 344-8.

Table 344-8 Treatment Goals for Adults with Diabetes

<table>
<thead>
<tr>
<th>Index</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemic control</td>
<td>Goal</td>
</tr>
<tr>
<td>A1C</td>
<td>&lt;7.0%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Preprandial capillary plasma glucose&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.9–7.2 mmol/L (70–130 mg/dL)</td>
</tr>
<tr>
<td>Peak postprandial capillary plasma glucose&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt;10.0 &lt;1.7 mmol/L (&lt;180 mg/dL)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Lipids&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>&lt;2.6 mmol/L (100 mg/dL)</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>&gt;1 mmol/L (40 mg/dL)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&gt;1.3 mmol/L (50 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>&lt;1.7 mmol/L (150 mg/dL)</td>
</tr>
</tbody>
</table>

<sup>a</sup>As recommended by the ADA; goals should be individualized for each patient (see text). Goals may be different for certain patients.

<sup>b</sup>A1C is primary goal.

<sup>c</sup>Normal range for A1C: 4.0–6.0% (DCCT-based assay).

<sup>d</sup>One–two hours after beginning of a meal.

<sup>e</sup>In decreasing order of priority.
The care of an individual with either type 1 or type 2 DM requires a multidisciplinary team. Central to the success of this team is enthusiasm, all of which are essential for optimal diabetes management. Members of the health care team include the primary care diabetologist, a certified diabetes educator, and a nutritionist. In addition, when the complications of DM arise, subspecialists (vascular surgeons, cardiologists, ophthalmologists, and podiatrists) with experience in DM-related complications are essential.

A number of names are sometimes applied to different approaches to diabetes care, such as intensive insulin therapy. The current chapter, and other sources, use the term comprehensive diabetes care to emphasize the fact that comprehensive diabetes care of both type 1 and type 2 DM requires a multidisciplinary approach. Employment-related issues may impact diabetes care. The International Diabetes Federation (IDF), recognizing that resources vary widely throughout the world, has issued guidelines for standard care (a well-developed service base and with health care funding based on their national wealth), minimal care (health care settings with very limited resources), and comprehensive care. This chapter provides guidance for this comprehensive level of diabetes care.

**Patient Education About DM, Nutrition, and Exercise**

The patient with type 1 or type 2 DM should receive education about nutrition, exercise, care of diabetes during illness, and management of complications. Along with improved compliance, patient education allows individuals with DM to assume greater responsibilities for their care. Patient education is an ongoing process with regular visits for reinforcement; it should not be a process that is completed after one or two visits to a health care provider. Patient education refers to education about the individualized management plan for the patient as diabetes self-management education (DSME). Management of type 2 DM may be improved by regularly monitoring blood glucose, physical activity, and weight reduction. Education and patient participation in the diabetes management team (electronic, telephone, etc.) improves glycemic control.

**DIABETES EDUCATION**

The diabetes educator is a health care professional (nurse, dietician, or pharmacist) with specialized patient education skills who provides education on diabetes management. Education topics important for optimal diabetes care include self-monitoring of blood glucose, insulin administration, guidelines for diabetes management during illnesses, prevention and management of hypoglycemia, and diabetes management before, during, and after exercise. The International Diabetes Federation (IDF) recommends that the diabetes education program include topics such as diabetes self-management, pharmacologic treatment, complications of diabetes, and prevention. The education program should be individualized and include topics specific to the individual's needs. The diabetes educator is also responsible for ensuring that the patient understands the importance of monitoring blood glucose levels and the role of insulin in the management of diabetes.

**NUTRITION**

Medical nutrition therapy (MNT) is a term used by the ADA to describe the optimal coordination of caloric intake with other aspects of diabetes management, such as medication, exercise, and lifestyle modifications. MNT is based on a comprehensive approach to diabetes management and is individualized to meet the needs of each patient. MNT includes the development of an individualized treatment plan that takes into account the patient's medical history, current health status, and lifestyle factors. The plan may include recommendations for weight loss, dietary changes, and physical activity. MNT is an important component of comprehensive diabetes care and is designed to help patients achieve their goals for glycemic control and overall health.

In general, the components of optimal MNT are similar for individuals with type 1 or type 2 DM and similar to those for the general population. The components of MNT include:

- **Nutrition Education**: This includes education about the principles of nutrition and how they apply to diabetes management. The patient is taught how to plan a diet that meets their nutritional needs while also controlling blood glucose levels.
- **Medication Management**: Patients are taught how to use their medications effectively and how to manage their diabetes medication regimen.
- **Physical Activity**: Patients are encouraged to engage in regular physical activity to help manage their diabetes.
- **Blood Glucose Monitoring**: Patients are taught how to monitor their blood glucose levels at home and how to use this information to adjust their treatment plan.
- **Counseling**: Patients receive ongoing counseling to help them manage their diabetes and make lifestyle changes.

MNT is designed to be a comprehensive, individualized approach to diabetes management that takes into account the unique needs of each patient.
diet with vitamins, antioxidants (vitamin C and E), or micronutrients (chromium) in patients with diabetes.

<table>
<thead>
<tr>
<th>Table 344-9 Nutritional Recommendations for Adults with Diabetes⁹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight loss diet (in prediabetes and type 2 DM)</strong></td>
</tr>
<tr>
<td>● Hypocaloric diet that is low-fat or low-carbohydrate</td>
</tr>
<tr>
<td><strong>Fat in diet</strong></td>
</tr>
<tr>
<td>● Minimal <em>trans</em> fat consumption</td>
</tr>
<tr>
<td><strong>Carbohydrate in diet</strong></td>
</tr>
<tr>
<td>● Monitor carbohydrate intake in regards to calories</td>
</tr>
<tr>
<td>● Sucrose-containing foods may be consumed with adjustments in insulin dose</td>
</tr>
<tr>
<td>● Amount of carbohydrate determined by estimating grams of carbohydrate in diet for (type 1 DM)</td>
</tr>
<tr>
<td>● Glycemic index reflects how consumption of a particular food affects the blood glucose</td>
</tr>
<tr>
<td><strong>Protein in diet:</strong> as part of an optimal diet</td>
</tr>
<tr>
<td><strong>Other components</strong></td>
</tr>
<tr>
<td>● Nonnutrient sweeteners</td>
</tr>
<tr>
<td>● Routine supplements of vitamins, antioxidants, or trace elements not advised</td>
</tr>
</tbody>
</table>

⁹See text for differences for patients with type 1 or type 2 diabetes. As for the general population, a healthy diet includes fruits, vegetables, and whole grains.

**Source:** Adapted from American Diabetes Association, 2011.

The goal of MNT in the individual with type 1 DM is to coordinate and match the caloric intake, both tempor insulin. MNT in type 1 DM and self-monitoring of blood glucose must be integrated to define the optimal ins utilize carbohydrate counting or exchange systems to estimate the nutrient content of a meal or snack. Bas a meal, an insulin-to-carbohydrate ratio determines the bolus insulin dose for a meal or snack. MNT must b regimen must allow for deviations in caloric intake. An important component of MNT in type 1 DM is to mini diabetes management.

The goals of MNT in type 2 DM should focus on weight loss and address the greatly increased prevalence of obesity) and disease in this population. The majority of these individuals are obese, and weight loss is stron Hypocaloric diets and modest weight loss (5–7%) often result in rapid and dramatic glucose lowering in indi studies document that long-term weight loss is uncommon. MNT for type 2 DM should emphasize modest calorie intake, and increased physical activity. Increased consumption of soluble, dietary fiber may improve glycem exercise improve insulin resistance.

**EXERCISE**

Exercise has multiple positive benefits including cardiovascular risk reduction, reduced blood pressure, mair loss. For individuals with type 1 or type 2 DM, exercise is also useful for lowering plasma glucose (during ar patients with diabetes, the ADA recommends 150 min/week (distributed over at least 3 days) of moderate i include resistance training.

Despite its benefits, exercise presents challenges for individuals with DM because they lack the normal glu glucagon rises during exercise). Skeletal muscle is a major site for metabolic fuel consumption in the restin aerobic exercise greatly increases fuel requirements. Individuals with type 1 DM are prone to either hypergl
pre-exercise plasma glucose, the circulating insulin level, and the level of exercise-induced catecholamines. This relative hyperinsulinemia may reduce hepatic glucose production (decreased glycogenolysis, decreased 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 if the blood glucose is >14 mmol/L (250 mg/dL) and ketones are present; (2) if the blood glucose is <5.6 mmol/L monitor glucose during exercise and ingest carbohydrate to prevent hypoglycemia; (3) decrease insulin doses during exercise; (4) learn individual glucose responses to different types of exercise depending on intensity and duration of exercise. In individuals with type 2 DM, exercise-related hypoglycemia is less common because asymptomatic cardiovascular disease appears at a younger age in both type 1 and type 2 DM, form individuals with any of the following: age >35 years, diabetes duration >15 years (type 1 DM) or >10 years (type 2 DM), PAD, other risk factors of CHD, or autonomic neuropathy. Because asymptomatic cardiovascular disease appears at a younger age in both type 1 and type 2 DM, form individuals with any of the following: age >35 years, diabetes duration >15 years (type 1 DM) or >10 years (type 2 DM), PAD, other risk factors of CHD, or autonomic neuropathy. Because asymptomatic cardiovascular disease appears at a younger age in both type 1 and type 2 DM, form individuals with any of the following: age >35 years, diabetes duration >15 years (type 1 DM) or >10 years (type 2 DM), PAD, other risk factors of CHD, or autonomic neuropathy. Because asymptomatic cardiovascular disease appears at a younger age in both type 1 and type 2 DM, form individuals with any of the following: age >35 years, diabetes duration >15 years (type 1 DM) or >10 years (type 2 DM), PAD, other risk factors of CHD, or autonomic neuropathy.

**Monitoring the Level of Glycemic Control**

Optimal monitoring of glycemic control involves plasma glucose measurements by the patient and an assessment of long-term glycemic control (HbA1c and review of the patient's self-measurements of plasma glucose). These measurements provide a picture of short-term glycemic control, whereas the A1C reflects average glycemic control over the previous 2-3 months.

**SELF-MONITORING OF BLOOD GLUCOSE**

Self-monitoring of blood glucose (SMBG) is the standard of care in diabetes management and allows the patient to measure capillary plasma glucose accurately and to assess glucose control in real time. SMBG, a small drop of blood and an easily detectable enzymatic reaction allow measurement of the capillary glucose at the fingertips; alternative testing sites (e.g., forearm) are less reliable, especially when the blood glucose is fluctuating rapidly. SMBG monitors are available, and the certified diabetes educator is critical in helping the patient select the best testing site (e.g., finger, earlobe) and providing education on how to interpret the glucose measurements with diet history, medication changes, and exercise history. The frequency of SMBG measurements must be individualized and adapted to address the goals of diabetes care. Those with type 2 DM taking multiple insulin injections each day should routinely measure their plasma glucose three or more times per day to assess short-acting insulin and to modify long-acting insulin doses. Most individuals with type 2 DM require less frequent monitoring, and if the blood glucose is well-controlled, one to two SMBG measurements per day (or fewer in patients who are on oral agents) is adequate. Measurements in individuals with type 1 or type 2 DM should be performed prior to a meal and supplement postprandial glucose targets (Table 344-8).

Devices for continuous blood glucose monitoring (CGM) have been approved by the FDA, and others are in various stages of development. These devices replace the need for traditional glucose measurements. This rapidly evolving technology requires substantial expertise on the part of the patient and the certified diabetes educator. Current continuous glucose-monitoring systems measure the glucose in interstitial fluid, which is in equilibrium with plasma glucose and provides useful short-term information about the patterns of glucose changes as well as an enhanced ability to detect hypoglycemia. Clinical experience with these devices is rapidly growing, and they are most suitable for individuals with type 1 diabetes who have not achieved glycemic targets despite major efforts. Ketones are an indicator of early diabetic ketoacidosis and should be measured in individuals with type 1 DM.
(300 mg/dL) during a concurrent illness or with symptoms such as nausea, vomiting, or abdominal pain. Blood testing with nitroprusside-based assays that measure only acetoacetate and acetone.

**ASSESSMENT OF LONG-TERM GLYCEMIC CONTROL**

Measurement of glycated hemoglobin is the standard method for assessing long-term glycemic control. When plasma glucose is increased in nonenzymatic glycation of hemoglobin; this alteration reflects the glycemic history over the previous 120 days (glycemic level in the preceding month contributes about 50% to the A1C value). There are multiple forms of glycated hemoglobin, and these have significant interassay variations; assays that are calibrated against the DCCT A1C assay methodology, hemoglobinopathies, anemias, reticulocytosis, transfusions, and uremia may interfere with the A1C result.

A1C should be measured in all individuals with DM during their initial evaluation and as part of their comprehensive diabetes care. The A1C should mirror, to a certain extent, the short-term measurements of recent intercurrent illnesses may impact the SMBG measurements but not the A1C. Likewise, postprandial plasma glucose values: an A1C of 6% = 7.0 mmol/L (126 mg/dL), 7% = 8.6 mmol/L (154 mg/dL), 8% = 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). In standardized plasma glucose values, measurement of the A1C at least twice per year. More frequent testing (every 3 months) is warranted when glycemic control has changed. The degree of glycation of other proteins, such as albumin, can be used as an alternative indicator of glycemic control.

Alternative assays of glycemic control should not be routinely used since studies demonstrating that it accurately predicts the outcome of diabetes complications (Fig. 344-8).

The ADA recommends measurement of the A1C at least twice per year. More frequent testing (every 3 months) is warranted when glycemic control has changed. The degree of glycation of other proteins, such as albumin, can be used as an alternative indicator of glycemic control.

**TYPE 1 DIABETES MELLITUS**

**General Aspects**

The ADA recommendations for fasting and bedtime glycemic goals and A1C targets are summarized in Table 344-8. Because individuals with type 1 DM partially or completely lack endogenous insulin secretion, basal insulin is essential for regulating glycogen breakdown, gluconeogenesis, lipolysis, and ketogenesis.
for the carbohydrate intake and promote normal glucose utilization and storage.

**Intensive Management**

Intensive diabetes management has the goal of achieving euglycemia or near-normal glycemia. This approach requires continuing patient education, comprehensive recording of plasma glucose measurements and nutrition intake by the patient, and choosing insulin regimens that match glucose intake and insulin dose. Insulin regimens usually include multiple-component insulin regimens (each discussed below).

The benefits of intensive diabetes management and improved glycemic control include a reduction in the microvascular complications of DM, which persists after a period of near-normoglycemia. From a psychological standpoint, the patient or his or her diabetes and often notes an improved sense of well-being, greater flexibility in the timing and content of meals, and the ability to exercise. In addition, intensive diabetes management prior to and during pregnancy reduces the risk of fetal malformations and management is strongly encouraged in newly diagnosed patients with type 1 DM because it may prolong the period of near-normoglycemia and a reduced risk of serious hypoglycemia.

Although intensive management confers impressive benefits, it is also accompanied by significant personal and financial costs to individuals.

**Insulin Preparations**

Current insulin preparations are generated by recombinant DNA technology and consist of the amino acid sequence of human insulin. In the United States, most insulin is formulated as U-100 (100 units/mL). Regular insulin formulated as U-500 (50 units/mL) is available for use in patients with severe insulin resistance. Human insulin has been formulated with distinctive pharmacokinetics or genetically modified to match secretion. Insulins can be classified as short-acting or long-acting (Table 344-10). For example, one short-acting analogue in which the 28th and 29th amino acids (lysine and proline) on the insulin B chain have been reversed is insulin glulisine. Aspart, lispro, or glulisine are other genetically modified insulin analogues with properties similar to lispro. These insulins allow for more rapid absorption and onset of action and a shorter duration of action. This allows entrainment of insulin injection and action to rising plasma glucose levels following meals. The short-acting insulins are preferred over regular insulin for prandial coverage. Insulin glargine is a long-acting analogue in which asparagine is replaced by glycine at amino acid 21, and two arginine residues are added to the C terminus. 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 nocturnal hypoglycemia, which has been reported with insulin glargine when compared to NPH insulin. The possible association between glargine and increased risk of hypoglycemia is controversial. Insulin detemir has a fatty acid side chain that prolongs its action, allowing entrainment of insulin injection and action to rising plasma glucose levels following meals. The shorter duration of action of detemir allows injections at bedtime, providing a reduced number of hypoglycemic episodes, primarily because the decay of insulin action corresponds to the decay of consumption.

| Table 344-10 Properties of Insulin Preparations
<table>
<thead>
<tr>
<th>Preparation</th>
<th>Time of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Onset, h</td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
</tr>
<tr>
<td>Aspart</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>Glulisine</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>Lispro</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>Regular</td>
<td>0.5–1.0</td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
</tr>
<tr>
<td>Preparation</td>
<td>Time of Action</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Detemir</td>
<td>Onset, h</td>
</tr>
<tr>
<td></td>
<td>1–4</td>
</tr>
<tr>
<td>Glargine</td>
<td>1–4</td>
</tr>
<tr>
<td>NPH</td>
<td>1–4</td>
</tr>
<tr>
<td>Insulin combinations</td>
<td></td>
</tr>
<tr>
<td>75/25–75% protamine lispro, 25% lispro</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>70/30–70% protamine aspart, 30% aspart</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>50/50–50% protamine lispro, 50% lispro</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>70/30–70% NPH, 30% regular</td>
<td>0.5–1</td>
</tr>
</tbody>
</table>

\(^a\)Glargine and detemir have minimal peak activity.

\(^b\)Dual: two peaks—one at 2–3 h and the second one several hours later.

**Source:** Adapted from JS Skyler, *Therapy for Diabetes Mellitus and Related Disorders*, American Diabetes A

Basal insulin requirements are provided by long-acting (NPH insulin, insulin glargine, or insulin detemir) ins acting insulin in an attempt to mimic physiologic insulin release with meals. Although mixing of NPH and sh mixing may alter the insulin absorption profile (especially the short-acting insulins). For example, lispro abs insulin absorption when the patient mixes different insulin formulations should not discourage mixing insulin (1) Mix the different insulin formulations in the syringe immediately before injection (inject within 2 min aft the same routine in terms of insulin mixing and administration to standardize the physiologic response to in detemir with other insulins. The miscibility of human regular and NPH insulin allows for the production of co (70/30), or equal mixtures of NPH and regular (50/50). Other combination insulin formulations are insulin a including the insulin analogue mixed with protamine, these combinations have a short-acting and long-actir patient (only two injections/day), combination insulin formulations do not allow independent adjustment of formulations are available as insulin "pens," which may be more convenient for some patients. Insulin deli investigation.

**Insulin Regimens**

Representations of the various insulin regimens that may be utilized in type 1 DM are illustrated in **Fig. 344** symmetric curves, there is considerable patient-to-patient variation in the peak and duration. In all regimer basal insulin, whereas regular, insulin aspart, glulisine, or lispro insulin provides prandial insulin. Short-actir min) or just after a meal; regular insulin is given 30–45 min prior to a meal.

**Figure 344-12**
Representative insulin regimens for the treatment of diabetes. For each panel, the y-axis shows the amount of insulin effect and with a vertical arrow. The type of insulin is noted above each insulin curve. A. A multiple-component insulin regimen required each day) to provide basal insulin coverage and three shots of glulisine, lispro, or insulin aspart to provide long-acting insulin (NPH) and short-acting insulin [glulisine, lispro, insulin aspart (solid red line), or regular (green dashed)] and a bolus injection at each meal. C. Insulin administration by insulin infusion device is shown with the basal insulin and a bolus injection at each meal. Increased slightly prior to the patient awakening in the morning. Glulisine, lispro, or insulin aspart is used in the insulin pump. Mellitus. American Diabetes Association, Alexandria, VA, 2004.]

A shortcoming of current insulin regimens is that injected insulin immediately enters the systemic circulation, whereas endogen venous system. Thus, exogenous insulin administration exposes the liver to subphysiologic insulin levels. No insulin regimen replicates the pattern of the pancreatic islet. However, the most physiologic regimens entail more frequent insulin injections, greater reliance frequent capillary plasma glucose measurements. In general, individuals with type 1 DM require 0.5–1 U/kg per day of insulin divided among the insulin given as basal insulin. Multiple-component insulin regimens refer to the combination of basal insulin and bolus insulin (preprandial short-acting insulin are altered to accommodate the SMBG results, anticipated food intake, and physical activity. Such regimens more flexibility in terms of lifestyle and the best chance for achieving near normoglycemia. One such regimen glargine or detemir and preprandial lispro, glulisine, or insulin aspart. The insulin aspart, glulisine, or lispro the preprandial glucose and the anticipated carbohydrate intake. To determine the meal component of the preprandial insulin dose, a common ratio for type 1 DM is 1–1.5 units/10 g of carbohydrate, but this must be det the supplemental or correcting insulin based on the preprandial blood glucose [one formula uses 1 unit of insulin for every 10 g of carbohydrate target; another formula uses (body weight in kg) x (blood glucose – desired glucose in mg/dL)/170 consists of bedtime NPH insulin, a small dose of NPH insulin at breakfast (20–30% of bedtime dose), and pr regimen are in use but have the disadvantage that NPH has a significant peak, making hypoglycemia more is absolutely essential for these types of insulin regimens.

One commonly used regimen consists of twice-daily injections of NPH mixed with a short-acting insulin before meals. These regimens usually prescribe two-thirds of the total daily insulin dose in the morning (with about two-thirds g and one-third before the evening meal (with approximately one-half given as long-acting insulin and one-half as short-acting insulin). It enforces a rigid schedule on the patient, in terms of daily activity and the content and timing of meals. All hyperglycemia, it does not generate near-normal glycemic control in individuals with type 1 DM. Moreover, activity is increased, hyperglycemia or hypoglycemia may result. Moving the long-acting insulin from before
hypoglycemia and provide more insulin as glucose levels rise in the early morning (so-called dawn phenomenon) based on SMBG results with the following general assumptions: (1) the fasting glucose is primarily determined by the prior even pre-lunch glucose is a function of the morning short-acting insulin; (3) the pre-supper glucose is a function of the pre-supper, short-acting insulin. This is not an optimal regimen for the patient with type 2 diabetes.

Continuous SC insulin infusion (CSII) is a very effective insulin regimen for the patient with type 1 diabetes. Insulin ("bolus") is delivered by the insulin infusion device based on instructions from the patient, who uses plasma glucose and anticipated carbohydrate intake (see above). These sophisticated insulin infusion devices require instruction by a health professional with considerable experience with insulin infusion device management team. Insulin infusion devices present unique challenges, such as infection at the infusion site becomes obstructed, or diabetic ketoacidosis if the pump becomes disconnected. Since most physicians use short half-life of these insulins quickly lead to insulin deficiency if the delivery system is interrupted. Essential to the safe use of education about pump function and frequent SMBG. Efforts to create a closed-loop system in which data from continuous glucose monitoring devices are used to adjust insulin delivery continue.

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 well established. The rationale that patients who are insulin deficient are also amylin deficient, an analogue of amylin (pramlintide) excursions in type 1 and type 2 diabetic patients taking insulin. Pramlintide injected just before a meal slows gastric emptying and alters meal-related glucose excursions. In type 1 diabetes, pramlintide is started as a 15-μg SC injection before each meal and may be titrated up to 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 90 μg. The effects are nausea and vomiting, and dose escalations should be slow to limit these side effects. Because pramlintide slows gastric emptying and should not be used in combination with other drugs that slow GI motility. The short-acting insulin initially be reduced to avoid hypoglycemia and then titrated as the effects of the pramlintide become evident sometimes used in conjunction in patients with type 1 DM.

TYPE 2 DIABETES MELLITUS

General Aspects

The goals of therapy for type 2 DM are similar to those in type 1. While glycemic control tends to dominate type 2 DM must also include attention to the treatment of conditions associated with type 2 DM (obesity, hypertension, dyslipidemia). Detection/management of DM-related complications (Fig. 344-13). DM-specific complications may be present in up to 20–50% of type 2 DM. Reduction in cardiovascular risk is of paramount importance as this is the leading cause of mortality and lipid goals (Table 344-8) should begin in concert with glucose-lowering interventions.

Figure 344-13
Essential elements in comprehensive diabetes care of type 2 diabetes.

Type 2 diabetes management should begin with MNT (discussed above). An exercise regimen to increase insulin sensitivity and instituted. Pharmacologic approaches to the management of type 2 DM include oral glucose-lowering agents, insulin, and other. Most physicians and patients prefer oral glucose-lowering agents as the initial choice (discussed below) after review of various glycemic control reduces "glucose toxicity" to the islet cells and improves endogenous insulin secretion. How requires multiple therapeutic agents and often insulin.

**Glucose-Lowering Agents**

Advances in the therapy of type 2 DM have generated oral glucose-lowering agents that target different pathophysiologic mechanisms of action, glucose-lowering agents are subdivided into agents that increase insulin secretion, enhance GLP-1 action (Table 344-11). Glucose-lowering agents other than insulin (with the exception of a in type 1 DM and should not be used for glucose management of severely ill individuals with type 2 DM. Ins 2 diabetes.

**Table 344-11 Agents Used for Treatment of Type 1 and Type 2 Diabetes**

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Examples</th>
<th>A1C Reduction (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Agent-Specific Advantages</th>
<th>Agent Disad</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanides&lt;sup&gt;b&lt;/sup&gt;</td>
<td>↓ Hepatic glucose production</td>
<td>Metformin</td>
<td>1–2</td>
<td>Weight neutral, Do not cause hypoglycemia, inexpensive</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Examples</td>
<td>A1C Reduction (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Agent-Specific Advantages</td>
<td>Agent-Specific Disadvantages</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------</td>
<td>-----------------------------</td>
<td>---------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors&lt;sup&gt;b&lt;/sup&gt;</td>
<td>↓ GI glucose absorption</td>
<td>Acarbose, Miglitol</td>
<td>0.5–0.8</td>
<td>Reduce postprandial glycemia</td>
</tr>
<tr>
<td>Dipeptidyl peptidase IV inhibitors&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Prolong endogenous GLP-1 action</td>
<td>Saxagliptin, Sitagliptin, Vildagliptin</td>
<td>0.5–0.8</td>
<td>Do not cause hypoglycemia</td>
</tr>
<tr>
<td>Insulin secretagogues: Sulfonylureas&lt;sup&gt;b&lt;/sup&gt;</td>
<td>↑ Insulin secretion</td>
<td>See text and Table 344-12</td>
<td>1–2</td>
<td>Inexpensive</td>
</tr>
<tr>
<td>Insulin secretagogues: Non-sulfonylureas&lt;sup&gt;b&lt;/sup&gt;</td>
<td>↑ Insulin secretion</td>
<td>See text and Table 344-12</td>
<td>1–2</td>
<td>Short onset of action, lower postprandial glucose</td>
</tr>
<tr>
<td>Thiazolidinediones&lt;sup&gt;b&lt;/sup&gt;</td>
<td>↓ Insulin resistance, ↑ glucose utilization</td>
<td>Rosiglitazone, Pioglitazone</td>
<td>0.5–1.4</td>
<td>Lower insulin requirements</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Bind bile acids; mechanism of glucose lowering not known</td>
<td>Colesevelam</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td><strong>Parenteral</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>↑ Glucose utilization, ↓ Hepatic glucose production, and other anabolic actions</td>
<td>See text and Table 344-10</td>
<td>Not limited</td>
<td>Known safety profile</td>
</tr>
<tr>
<td>GLP-1 receptor agonists&lt;sup&gt;b&lt;/sup&gt;</td>
<td>↑ Insulin, ↓ glucagon, slow gastric emptying, satiety</td>
<td>Exenatide, liraglutide</td>
<td>0.5–1.0</td>
<td>Weight loss, do not cause hypoglycemia</td>
</tr>
<tr>
<td>Amylin agonists&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>Slow gastric emptying, ↓ glucagon</td>
<td>Pramlintide</td>
<td>0.25–0.5</td>
<td>Reduce postprandial glycemia; weight loss</td>
</tr>
<tr>
<td><strong>Medical nutrition therapy and physical activity</strong>&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>↓ Insulin resistance, ↑ insulin secretion</td>
<td>Low-calorie, low-fat diet, exercise</td>
<td>1–3</td>
<td>Other health benefits</td>
</tr>
</tbody>
</table>
A1C reduction (absolute) depends partly on starting A1C.

Used for treatment of type 2 diabetes.

Used in conjunction with insulin for treatment of type 1 diabetes.

**Biguanides**

Metformin, representative of this class of agents, reduces hepatic glucose production and improves peripheral glucose utilization. Metformin activates AMP-dependent protein kinase and enters cells through organic cation transporters (polymorphism). Metformin reduces fasting plasma glucose and insulin levels, improves the lipid profile, and promotes moderate weight loss. The daily dose can be increased to 1000 mg bid. An extended-release form is available and may have fewer gastrointestinal side effects. Because of its relatively slow onset of action and gastrointestinal symptoms with higher doses, the dose should be increased based on SMBG measurements. Metformin is effective as monotherapy and can be used in combination with other oral agents. Lactic acidosis is very rare and can be prevented by careful patient selection. Vitamin B12 levels are 30% lower during metformin use. Patients with renal insufficiency (GFR < 60 mL/min), any form of acidosis, CHF, liver disease, or severe hypoxemia, or patients who are seriously ill, in patients who can take nothing orally, and in those receiving radiographic contrast agents should 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 or in individuals with type 2 DM of relatively recent onset (<5 years), who have residual endogenous insulin production. Tolazamide, tolbutamide; not shown in Table 344-12) have a longer half-life, a greater incidence of hypoglycemia, and are rarely used. Second-generation sulfonylureas have a more rapid onset of action and better coverage of the postprandial glucose. First-generation agents may require more than once-a-day dosing (Table 344-12). Sulfonylureas reduce both fasting and postprandial glucose levels, though, the insulin release is more sustained. Glimepiride and glipizide can be given in a single daily dose and are preferred. Nateglinide are not sulfonylureas but also interact with the ATP-sensitive potassium channel. Because of the immediacy of the effect, these agents may require more than once-a-day dosing.

**Table 344-12 Properties of Insulin Secretagogues**

<table>
<thead>
<tr>
<th>Class/Generic Name</th>
<th>Daily Dosage, mg</th>
<th>Duration of Action, h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>1–8</td>
<td>24</td>
</tr>
<tr>
<td>Glipizide</td>
<td>5–40</td>
<td>12–18</td>
</tr>
<tr>
<td>Glipizide (extended release)</td>
<td>5–20</td>
<td>24</td>
</tr>
<tr>
<td>Glyburide</td>
<td>1.25–20</td>
<td>12–24</td>
</tr>
<tr>
<td>Glyburide (micronized)</td>
<td>0.75–12</td>
<td>12–24</td>
</tr>
<tr>
<td><strong>Nonsulfonylureas (Meglititinides)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>0.5–16</td>
<td>2–6</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>180–360</td>
<td>2–4</td>
</tr>
<tr>
<td><strong>GLP-1 agonist</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>0.01–0.02</td>
<td>4–6</td>
</tr>
</tbody>
</table>
### Class/Generic Name

<table>
<thead>
<tr>
<th>Class/Generic Name</th>
<th>Daily Dosage, mg</th>
<th>Duration of Action, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>0.6–1.8</td>
<td>12–24</td>
</tr>
<tr>
<td><strong>Dipeptidyl Peptidase-4 Inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>2.5–5</td>
<td>12–16</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100</td>
<td>12–16</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>50–100</td>
<td>12–24</td>
</tr>
</tbody>
</table>

**Abbreviation:** GLP-1, glucagon-like peptide 1.

These insulin secretagogues are generally well tolerated. These agents, 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 ingestion, or renal dysfunction is not advisable. Weight gain, a common side effect of sulfonylurea therapy, results from increased insulin secretion. Some sulfonylureas have significant drug interactions with alcohol and some medications including warfarin, aspirin, and fluconazole. A related isoform of ATP-sensitive potassium channels is present in the myocardium and the brain. All of these agents have affinity for this isoform. Despite concerns that this agent might affect the myocardial response to ischemia and observational studies in type 2 DM, studies have not shown an increased cardiac mortality with glyburide.

### Insulin Secretagogues—Agents that Enhance GLP-1 Receptor Signaling

"Incretins" amplify glucose-stimulated insulin secretion (Fig. 344-4). Agents that either act as a GLP-1 agonist or enhance endogenous GLP-1 function are useful in the treatment of type 2 diabetes (Table 344-12). Agents in this class do not cause hypoglycemia because of their glucose dependence. Agents in this class, such as exenatide, are approved for use as monotherapy and for use as combination therapy with metformin. Insulin secretagogues are generally well tolerated. The major side effects are nausea, vomiting, and diarrhea; pancreatitis and reduced renal function may also occur. Whether GLP-1 receptor agonists enhance beta cell survival, promote beta cell proliferation, or increase cardiovascular risk, studies have not shown an increased cardiac mortality with glyburide.

### α-Glucosidase Inhibitors

α-Glucosidase inhibitors (acarbose and miglitol) reduce postprandial hyperglycemia by delaying glucose absorption (Table 344-11). Postprandial hyperglycemia, secondary to impaired hepatic and peripheral glucose disposal, contributes to the metabolic state in type 2 DM. These drugs, taken just before each meal, reduce glucose absorption by inhibiting the enzyme that cleaves carbohydrates into absorbable glucose and maltose.
the intestinal lumen. Therapy should be initiated at a low dose (25 mg of acarbose or miglitol) with the evening meal and may be increased delivery of oligosaccharides to the large bowel and can be reduced somewhat by gradual upward of sulfonylureas and increase the incidence of hypoglycemia. Simultaneous treatment with bile acid resins a used in individuals with inflammatory bowel disease, gastroparesis, or a serum creatinine >177 μmol/L (2 n agents in lowering the A1C but is unique because it reduces the postprandial glucose rise even in individual treatments occurs while taking these agents, the patient should consume glucose since the degradation anc

**Thiazolidinediones**

Thiazolidinediones reduce insulin resistance by binding to the PPAR-γ (peroxisome proliferator-activated receptor gamma) and the retinoid X receptor. The PPAR-γ receptor is found at highest levels in adipocytes but is expressed at low in many other tissues. These agents promote adipocyte differentiation, reduce hepatic fat accumulation, and adipogenesis. Thiazolidinediones promote a redistribution of fat from central to peripheral locations. Circulating insulin levels decrease with use of this class of drugs, troglitazone, was withdrawn from the U.S. market and is no longer available. Although rosiglitazone and pioglitazone do increase the A1C but is unique because it reduces the postprandial glucose rise even in individual patients consuming glucose since the degradation and absorption of carbohydrates is reduced somewhat by gradual upward dose titration.

Rosiglitazone raises LDL, HDL, and triglycerides slightly. Pioglitazone raises HDL to a greater degree and LDL reduction in insulin resistance. Although direct comparisons are not available, the two currently available th th the retinoid X receptor). The PPAR-γ receptor is found at highest levels in adipocytes but is expressed at lo regulate a large number of genes, promote adipocyte differentiation, reduce hepatic fat accumulation, and adipogenesis. Thiazolidinediones promote a redistribution of fat from central to peripheral locations. Circulating insulin levels decrease with the use of this class of drugs, troglitazone, was withdrawn from the U.S. market and is no longer available. Although rosiglitazone and pioglitazone do increase the A1C but is unique because it reduces the postprandial glucose rise even in individual patients consuming glucose since the degradation and absorption of carbohydrates is reduced somewhat by gradual upward dose titration.

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**Bile acid–binding resins**

Bile acid metabolism is abnormal type 2 diabetes. The bile acid–binding resin colesvelam has been approved for treatment of hypercholesterolemia. Emerging evidence indicates that bile acids, by signaling through nuclear receptors, may play a role in the regulation of insulin sensitivity. Bile acid–binding resins are minimally absorbed into the systemic circulation, how bile acid–binding resins lower cholesterol (oral solution and as 625-mg tablets) is prescribed as 3–6 tablets prior to meals. The most common side effects are gastrointestinal pain, and nausea. Bile acid–binding resins can increase plasma triglycerides and should be used cautiously since the safety of thiazolidinediones in pregnancy is not established.

**Other Therapies for Type 2 Diabetes**

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Recent concerns about increased cardiovascular risk associated with rosiglitazone have led to considerable changes in treatment strategy. The role of this class of drugs in the treatment of type 2 diabetes is uncertain.

**Bromocriptine**

A formulation of the dopamine receptor agonist bromocriptine (Cycloset), has been approved by the FDA for the treatment of hyperprolactinemia. However, this formulation is not available in the United States, and its role in the treatment of type 2 diabetes is uncertain.

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**Insulin Therapy in Type 2 DM**

Insulin should be considered as the initial therapy in type 2 DM, particularly in lean individuals or those with hepatic disease that precludes oral glucose-lowering agents, or in individuals who are hospitalized or acutely ill. Insulin therapy number of individuals with type 2 DM because of the progressive nature of the disorder and the relative insulin deficiency that diabetes. Both physician and patient reluctance often delay the initiation of insulin therapy, but glucose control and patient well-being patients who have not reached the glycemic target.

Because endogenous insulin secretion continues and is capable of providing some coverage of mealtime caloric intake, long-acting insulin (0.3–0.4 U/kg per day), given either before breakfast and in the evening (NPH) or just before bedtime (NPH, hyperglycemia and increased hepatic glucose production are prominent features of type 2 DM, bedtime insulin is more effective morning insulin. Glargine given at bedtime has less nocturnal hypoglycemia than NPH insulin. Some physicians prefer a relative insulin (5–15 units) to reduce the chance of hypoglycemia in the initial treatment period. The insulin dose in SMBG results. Both morning and bedtime long-acting insulin may be used in combination with oral glucose-lowering agents, but more often prandial insulin coverage with multiple insulin injections is needed as diabetes progresses. Formulations that have a combination of short-acting and long-acting insulin (Table 344-10) are sometimes used in patients with type 2 DM (usually insulin deficient as defined by C-peptide level), insulin secretagogues, biguanides, α-glucosidase inhibitors, thiazolidinediones, GLP-1 receptor agonists, DPP-IV inhibitors, GLP-1 receptor agonists, and thiazolidinediones improve glycemic control to a similar degree (1–2% reduction in A1C). (2) Assuming a similar degree of glycemic improvement, no clinical advantage to demonstrating, and any therapy that improves glycemic control is likely beneficial; (3) insulin secretagogues-glucosidase inhibitors begin to lower the plasma glucose immediately, whereas the glucose-lowering effects of the biguanides appear several weeks; (4) not all agents are effective in all individuals with type 2 DM (primary failure); (5) biguanides, DPP-IV inhibitors, and thiazolidinediones do not directly cause hypoglycemia; and (6) most individuals will eventually require oral glucose-lowering agents or insulin, reflecting the progressive nature of type 2 DM; (7) durability of glycemic control is slight.

**Choice of Initial Glucose-Lowering Agent**

The level of hyper-glycemia should influence the initial choice of therapy. Assuming maximal benefit of MNT with mild to moderate hyperglycemia [FPG <11.1–13.9 mmol/L (200–250 mg/dL)] often respond well to a single agent; severe hyperglycemia [FPG >13.9 mmol/L (250 mg/dL)] may respond partially but are unlikely to achieve remission that starts with a single agent and adds a second agent to achieve the glycemic target can be used (see “Combination therapy in individuals with severe hyperglycemia [FPG >13.9–16.7 mmol/L (250–300 mg/dL)] or in those who do not yet have achieved glycemic target. Treatment plans that are based on the rationale that more rapid glycemic control will reduce "glucose toxicity" to the islet cells, insulin is the 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, and GLP-1 receptor agonists, and thiazolidinediones improve glycemic control to a similar degree (1) insulin secretagogues-glucosidase inhibitors and DPP-IV inhibitors; (2) Assuming a similar degree of glycemic improvement, no clinical advantage to demonstrating, and any therapy that improves glycemic control is likely beneficial; (3) insulin secretagogues-glucosidase inhibitors begin to lower the plasma glucose immediately, whereas the glucose-lowering effect appears several weeks; (4) not all agents are effective in all individuals with type 2 DM (primary failure); (5) biguanides, DPP-IV inhibitors, and thiazolidinediones do not directly cause hypoglycemia; and (6) most individuals will eventually require oral glucose-lowering agents or insulin, reflecting the progressive nature of type 2 DM; (7) durability of glycemic control is slight.

Considerable clinical experience exists with metformin and sulfonylureas because they have been available for several decades. Metformin has the advantage that it promotes mild weight loss, lowers insulin levels, and improves glycemic control, although long-term data are not yet available. The thiazolidinediones are theoretically attractive because they improve insulin sensitivity, which is an abnormality in type 2 DM, namely insulin resistance. However, all of these agents are currently more costly. A reasonable treatment algorithm for initial therapy uses metformin as initial therapy because of its efficacy (344-14). Metformin has the advantage that it promotes mild weight loss, lowers insulin levels, and improves glycemic control, although long-term data are not yet available. The thiazolidinediones are theoretically attractive because they improve insulin sensitivity, which is an abnormality in type 2 DM, namely insulin resistance. However, all of these agents are currently more costly. A reasonable treatment algorithm for initial therapy uses metformin as initial therapy because of its efficacy (344-14). Metformin has the advantage that it promotes mild weight loss, lowers insulin levels, and improves glycemic control, although long-term data are not yet available. The thiazolidinediones are theoretically attractive because they improve insulin sensitivity, which is an abnormality in type 2 DM, namely insulin resistance. However, all of these agents are currently more costly. A reasonable treatment algorithm for initial therapy uses metformin as initial therapy because of its efficacy (344-14). Metformin has the advantage that it promotes mild weight loss, lowers insulin levels, and improves glycemic control, although long-term data are not yet available. The thiazolidinediones are theoretically attractive because they improve insulin sensitivity, which is an abnormality in type 2 DM, namely insulin resistance. However, all of these agents are currently more costly. A reasonable treatment algorithm for initial therapy uses metformin as initial therapy because of its efficacy (344-14).
Glycemic management of type 2 diabetes. See text for discussion of treatment of severe hyperglycemia or symptomatic hyperglycemia. Agents that can be added to metformin include insulin secretagogues, thiazolidinediones, α-glucosidase inhibitors, DPP-IV inhibitors, and GLP-1 receptor agonists.

Combination Therapy with Glucose-Lowering Agents

A number of combinations of therapeutic agents are successful in type 2 DM, and the dosing of agents in combination is the same. Because mechanisms of action of the first and second agents used are different, the effect on glycemic control is usually additive. Various combinations of oral agents are available, but evidence that they are superior to titration of single agents to a maximum dose and then addition of a third agent (based on reassessment of the A1C every 3 months) is not achieved with the combination of two agents (Fig. 344-14).

Treatment with insulin becomes necessary as type 2 DM enters the phase of relative insulin deficiency (as seen in long-standing glycemic control with one or two oral glucose-lowering agents. Insulin alone or in combination should be used. For example, a single dose of long-acting insulin at bedtime is effective in combination with metformin. As endogenous insulin production of long-acting and short-acting insulin regimens are necessary to control postprandial glucose excursions.
short-acting combination regimens discussed above for type 1 DM. Since the hyper-glycemia of type 2 DM tends to be more "stable" due to the underlying mechanisms of type 2 DM, insulin doses may need to be increased in 10% increments every 2–3 days using the FBG results. The daily insulin dose required can become quite large (1–2 units/kg body weight) as the insulin production falls and insulin resistance persists. Individuals who require >1 unit/kg per day of long-acting insulin, such as a thiazolidinedione or metformin, should be considered for even higher dosages. The addition of metformin or a thiazolidinedione can reduce insulin requirements, maintaining or even improving glycemic control. Insulin plus a thiazolidinedione promotes weight gain and insulin plus metformin may necessitate a reduction in the insulin dose to avoid hypoglycemia.

EMERGING THERAPIES

Whole pancreas transplantation (performed concomitantly with a renal transplant) may normalize glucose tolerance and is an option for patients with type 1 DM with ESRD, though it requires substantial expertise and is associated with the side effects of immunosuppression by limitations in pancreatic islet supply and graft survival and remains an area of clinical investigation. Many patients with type 1 DM also require small amounts of insulin or have insulin-positive cells within the pancreas. This suggests that beta cells may regenerate through an autoimmune process. Thus, efforts to suppress the autoimmune process and to stimulate beta cell regeneration are being tested in many clinical trials. Efforts to induce hard-won remission in patients who have been diagnosed with type 1 DM for several years after the diagnosis of type 1 DM. Closed-loop pumps that infuse the appropriate amount of insulin in response to changes in glucose levels are now available. New therapies under development for type 2 diabetes include activators of glucokinase, an inhibitor of 11β-hydroxysteroid dehydrogenase-1, and salsalate. Bariatric surgery for markedly obese individuals with type 2 diabetes has shown considerable promise—sometimes with resolution of diabetes without the need for insulin. The ADA clinical guidelines state that bariatric surgery should be considered for patients with a BMI >35 kg/m².
COMPLICATIONS OF THERAPY FOR DIABETES MELLITUS

As with any therapy, the benefits of efforts directed toward glycemic control must be balanced against the risks of treatment. 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. 345. Severe, recurrent hypoglycemia warrants examination of treatment regimen and glycemic goal for the individual patient. Weight gain occurs with most (insulin, insulin secretagogues, thiazolidine-diones) but not all (metformin, α-glucosidase inhibitors, GLP-1 receptor agonists, DPP-IV inhibitors) therapies that improve glycemic control. The weight gain is partially due to the anabolic effects of insulin and the reduction in glucosuria. In the DCCT, individuals with the greatest weight gain exhibited increases in LDL cholesterol and triglycerides as well as increases in blood pressure (both systolic and diastolic) similar to those seen in individuals with type 2 DM and insulin resistance. These effects could increase the risk of cardiovascular disease. As discussed previously, transient worsening of diabetic retinopathy or neuropathy sometimes accompanies improved glycemic control. As a result of recent controversies about the optimal glycemic goal and concerns about safety, the FDA now requires information about the cardiovascular safety profile as part of its new evaluation for treatment of type 2 diabetes.
ONGOING ASPECTS OF COMPREHENSIVE DIABETES CARE

The morbidity and mortality rates of DM-related complications can be greatly reduced by timely and consistent surveillance procedures (Table 344-13). These screening procedures are indicated for all individuals with DM, but many individuals with diabetes do not receive comprehensive diabetes care. Screening for dyslipidemia and hypertension should be performed annually. In addition to routine health maintenance, individuals with diabetes should also receive the pneumococcal and tetanus vaccines (at recommended intervals) and the influenza vaccine (annually). As discussed above, aspirin therapy should be considered in many patients with diabetes (primary prevention in type 1 or type 2 DM men >50 years or women >60 years with one risk factor CV disease), but its role in primary prevention in low-risk individuals is uncertain and not recommended.

### Table 344-13 Guidelines for Ongoing Medical Care for Patients with Diabetes

- Self-monitoring of blood glucose (individualized frequency)
- A1C testing (2–4 times/year)
- Patient education in diabetes management (annual)
- Medical nutrition therapy and education (annual)
- Eye examination (annual)
- Foot examination (1–2 times/year by physician; daily by patient)
- Screening for diabetic nephropathy (annual; see Fig. 344-11)
- Blood pressure measurement (quarterly)
- Lipid profile and serum creatinine (estimate GFR) (annual)
- Influenza/pneumococcal immunizations
- Consider antiplatelet therapy (see text)

**Abbreviation:** A1C, hemoglobin A1C.

An annual comprehensive eye examination should be performed by a qualified optometrist or ophthalmologist. If abnormalities are detected, further evaluation and treatment require an ophthalmologist skilled in diabetes-related eye disease. Because many individuals with type 2 DM have had asymptomatic diabetes for several years before diagnosis, the ADA recommends the following ophthalmologic examination schedule: (1) individuals with type 1 DM should have an initial eye examination within 5 years of diagnosis, (2) individuals with type 2 DM should have an initial eye examination at the time of diabetes diagnosis, (3) women with DM who are pregnant or contemplating pregnancy should have an eye examination prior to conception and during the first trimester, and (4) if eye exam is normal, repeat examination in 2–3 years may be appropriate.
An annual foot examination should (1) assess blood flow, sensation (monofilament testing, pin prick, or tuning fork), 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 neuropathy 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 includes testing for loss of protective sensation (LOPS) using monofilament testing plus one of the following tests: vibration, pinprick, ankle reflexes, or vibration perception threshold (using a biothesiometer). If the monofilament test or one of the other tests is abnormal, the patient is diagnosed with LOPS and counseled accordingly. Calluses and nail deformities should be treated by a podiatrist; the patient should be discouraged from self-care of even minor foot problems but should be strongly encouraged to check his or her feet daily for any early lesions. Providers should consider screening for asymptomatic peripheral arterial disease using ankle-brachial index testing in high-risk individuals.

An annual microalbuminuria measurement (albumin-to-creatinine ratio in spot urine) is advised in individuals with type 1 or type 2 DM (Fig. 344-10). The urine protein measurement in a routine urinalysis does not detect these low levels of albumin excretion (microalbuminuria). Screening for microalbuminuria should commence 5 years after the onset of type 1 DM and at the time of diagnosis of type 2 DM. Regardless of protein excretion results, the GFR should be estimated using the serum creatinine in all patients on an annual basis.
SPECIAL CONSIDERATIONS IN DIABETES MELLITUS

Psychosocial Aspects

Because the individual with DM can face challenges that affect many aspects of daily life, psychosocial assessment and treatment are a critical part of providing comprehensive diabetes care. The individual with DM must accept that he or she may develop complications related to DM. Even with considerable effort, normoglycemia can be an elusive goal, and solutions to worsening glycemic control may not be easily identifiable. The patient should view him- or herself as an essential member of the diabetes care team and not as someone who is cared for by the diabetes management team. Emotional stress may provoke a change in behavior so that individuals no longer adhere to a dietary, exercise, or therapeutic regimen. This can lead to the appearance of either hyper- or hypoglycemia. Eating disorders, including binge eating disorders, bulimia, and anorexia nervosa, appear to occur more frequently in individuals with type 1 or type 2 DM (Chap. 79).

Management in the 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 A1C. Electrolytes, renal function, and intravascular volume status should be assessed as well. The high prevalence of cardiovascular disease in individuals with DM (especially in type 2 DM) may require preoperative cardiovascular evaluation.

The goals of diabetes management during hospitalization are near-normoglycemia, avoidance of hypoglycemia, and transition back to the outpatient diabetes treatment regimen. 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 (NICE-SUGAR) of individuals in the intensive care unit (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 BG of 4.5–6 mmol/L or 81–108 mg/dL] compared to individuals with a more moderate glycemic goal (mean blood glucose of 8 mmol/L or 144 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 these glycemic goals for hospitalized patients: (1) in critically ill patients: glucose of 7.8–10.0 mmol/L or 140–180 mg/dL; (2) in non–critically ill patients: pre-meal glucose <7.8 mmol/L (140 mg/dL) and at other times BG <10 mmol/L (180 mg/dL).

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. Measures to reduce or prevent hypoglycemia include frequent glucose monitoring and anticipating potential modifications of insulin/glucose administration because of changes in the clinical situation or treatment (tapering of glucocorticoids, etc.) or interruption of enteral or parenteral infusions or PO intake.

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. 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. Regular insulin is preferred over insulin analogues for IV insulin infusion since it is less expensive and equally effective. The physician must consider carefully the clinical setting in which an insulin infusion will be utilized, including whether adequate ancillary personnel are available to monitor the plasma glucose frequently and whether they can adjust the insulin infusion rate to maintain the plasma 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) 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). The use of "sliding scale," short-acting insulin alone, where no insulin is given unless the blood glucose is elevated, is inadequate for in-patient glucose management and should not be used. The short-acting, preprandial insulin dose should include coverage for food consumption (based on anticipated carbohydrate intake) plus a corrective or supplemental insulin based on the patient’s insulin sensitivity and the blood glucose. For example, if the patient is thin (and likely insulin-sensitive), a corrective insulin supplement 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 supplement 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 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). The hospital diet should be determined by a nutritionist; terms such as ADA diet or low-sugar diet are no longer used.
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 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 in the 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 and performed under local or regional anesthesia, a reduced dose of SC, long-acting insulin may suffice (30–50% reduction, with short-acting insulin withheld or reduced). This approach facilitates the transition back to long-acting insulin after the procedure. Glucose may be infused to prevent hypoglycemia. 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 (25–50% reduction depending on clinical setting) plus preprandial, short-acting insulin. Oral glucose-lowering agents should be discontinued upon admission 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). Metformin should be withheld when radiographic contrast media will be given or if severe CHF, acidosis, or declining renal function is present.

**TOTAL PARENTERAL NUTRITION**

(See also Chap. 76.) Total parenteral nutrition (TPN) greatly increases insulin requirements. In addition, individuals not previously known to have DM may become hyperglycemic during TPN and require insulin treatment. 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, insulin may be added directly to the TPN solution or, preferably, given as a separate infusion. Often, individuals receiving either TPN or enteral nutrition receive their caloric loads continuously and not at "meal times"; consequently, SC insulin regimens must be adjusted.

**GLUCOCORTICOIDS**

Gluocorticoids 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 diabetes in other individuals ("steroid-induced diabetes"). The effects of gluocorticoids on glucose homeostasis are dose-related, usually reversible, and most pronounced in the postprandial period. If the FPG is near the normal range, oral diabetes agents (e.g., sulfonylureas, metformin) may be sufficient to reduce hyperglycemia. If the FPG >11.1 mmol/L (200 mg/dL), oral agents are usually not efficacious and insulin therapy is required. Short-acting insulin may be required to supplement long-acting insulin in order to control postprandial glucose excursions.

**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 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% of pregnancies in the United States. The incidence of GDM is greatly increased in certain ethnic groups, including African Americans 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 with increased risk for GDM (≥25 years; obesity; family history of DM; member of an ethnic group such as Latina, Native American, Asian American, African American, or Pacific Islander). 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. However, most physicians use insulin to treat GDM. 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. 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 diabetes management and normalization of the A1C are essential for individuals with existing DM who are planning pregnancy. 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 plasma glucose during the preconception period and throughout the periods of organ development in the fetus should be the goal.

**Lipodystrophic DM**

Lipodystrophy, or the loss of subcutaneous fat tissue, may be generalized in certain genetic conditions such as leprechaunism. Generalized lipodystrophy is associated with severe insulin resistance and is often accompanied by acanthosis nigricans and dyslipidemia. Localized lipodystrophy associated with insulin injections has been reduced considerably by the use of human insulin.

**PROTEASE INHIBITORS AND LIPODYSTROPHY**

Protease inhibitors used in the treatment of HIV disease (Chap. 189) 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), 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 by some undefined mechanism, since some features of the syndrome were observed before the introduction of protease inhibitors. Therapy for HIV-related lipodystrophy is not well established.
FURTHER READINGS


Chan JC et al: Diabetes in Asia: Epidemiology, risk factors, and pathophysiology. JAMA 301:2129, 2009 [PMID: 19470990]


