34 Diabetes Mellitus

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CHAPTER OUTLINE

Introduction

Diabetes mellitus is a heterogeneous group of disorders with distinct genetic, etiologic, immunologic, and pathophysiologic mechanisms that result in glucose intolerance and hyperglycemia. Patients with diabetes develop insulin deficiency, impaired peripheral insulin action, or both. Chronic exposure to hyperglycemia, glycemic variability, and resultant oxidative stress in genetically prone individuals can result in both acute (diabetic ketoacidosis [DKA] and hypoglycemia) and long-term (micro- and macrovascular) complications.

Diabetes is currently classified into four major types on the basis of etiology and clinical presentation:

1. **Type 1 diabetes (T1DM):** characterized by a gradual loss of insulin-producing pancreatic β-cells secondary to autoimmune destruction
2. **Type 2 diabetes (T2DM):** genetically predisposed individuals develop a chronic progressive disease characterized by insulin resistance and subsequent β-cell failure
3. **Gestational diabetes mellitus (GDM):** defined as hyperglycemia with onset or first recognition during pregnancy
4. **Other specific types,** including monogenetic forms of diabetes (i.e., neonatal diabetes and maturity onset diabetes of the young), diabetes attributable to diseases of the exocrine pancreas (i.e., cystic fibrosis), other endocrinopathies, and drug-induced diabetes (e.g., steroids) (American Diabetes Association [ADA], 2011a)

The prevalence of diabetes is increasing throughout the Western world. The World Health Organization estimates that more than 347 million people worldwide currently have diabetes, and 90% of all cased involve T2DM (ADA, 2011a; World Health Organization, 2013). This number is projected to grow to 439 million individuals worldwide (7.7% of the population) by 2030 (Shaw et al., 2010).

HISTORICAL OVERVIEW

In 1920, diabetes was a terminal disease with a life expectancy of 6 to 12 months (Bliss, 1982). Its treatment consisted of restricting caloric intake to less than 500 calories per day. Individuals who breached that nutrition threshold in an attempt to appease their hunger would develop DKA and die within hours to days. Life for patients with diabetes in the early 1900s was, in a word, miserable. Patients suffered from malnutrition, cataracts, blindness, gangrene, impotence, and immune-resistant infections (e.g., pneumonia, tuberculosis, boils, and carbuncles). Surgeons recognized the futility of operating on gangrenous, rotting legs; patients were equally likely to die from surgical complications as from the underlying infection. Women who were able to conceive were unable to carry their macrosomic babies to term. The "sickish sweet smell of rotten apples" breeched the halls of hospital wards as dehydrated patients with DKA lay hopelessly waiting to die (Bliss, 1982). All too often, death from diabetes would be considered a blessing by those who long suffered the consequences of chronic hyperglycemia.

The first human injection of insulin (derived from extracts obtained from dog pancreases) was given to a 14-year-old patient named Leonard Thompson in Toronto, Canada, on January 11, 1922. Weighing only 64 lb on admission, this "hopeless charity case" who was near death from DKA received a 7.5-cc injection of "thick black muck" in each hip (Bliss, 1982). The dose was calculated by Dr. Frederick Banting, who discovered insulin, and his medical student Charles Best based on their work with pancreatectomized dogs. Thompson nearly died from boils and sepsis because the "iletin" extract was impure and unsterile. Yet, to the amazement of all in attendance, his blood glucose level declined from 420 mg/dL to 330 mg/dL. Shortly after the pancreatic extract was purified, Thompson received additional injections. He was eventually discharged from the hospital and later died at 27 years of age secondary to complications from pneumonia.

In October 1922, another patient, Elsie Needham, became the first individual to ever have DKA reversed with the use of insulin. Although insulin was in short supply, physicians such as Eliot Joslin used the drug successfully to treat patients who were starving or dying of acute diabetes complications. Although the insulin extract had an immediate effect on reducing mortality, Joslin professed that lifestyle intervention remained the foundation of care for all individuals with diabetes.

Thus, less than a century ago, the discovery of insulin saved the lives of millions of people with diabetes while changing the process through which medicine is studied and practiced to this day. In short order, drug purification

methods were developed and perfected. The field of endocrinology was born. Other hormones were discovered and purified. Pharmaceutical companies began to fund clinical trials, allowing clinicians and scientists the opportunity to evaluate the safety and efficacy of new compounds.

Before 1920, clinicians relied on their own marketing skills to sell their homemade snake oil products from horse-drawn buggies. Various folkloric remedies, which rarely worked, were available to anyone and promoted to "cure whatever ails you." People were becoming skeptical about the practice of medicine, as well as about those who claimed to be experts at curing diseases such as diabetes, tuberculosis, senility, and sexually transmitted diseases. Doctors had not yet gained the public's trust in them as healers. After all, what could these men actually heal?

After the discovery of insulin was solidified, Banting refused to take the traditional approach of proclaiming his findings to the news media. Instead, he took the then-unprecedented route of publishing his data in a reputable medical journal (Banting and Best, 1922). People slowly began to trust physicians, not merely as quasi-mystical healers but as practitioners who could identify and cure disease through scientific discovery. Importantly, however, as Eliot Joslin noted in 1923, "Insulin is not a cure for diabetes" (Bliss, 1982).

By 1945, the lifespan of patients with diabetes had increased by nearly 45 years. Starvation and DKA gave way to long-term micro- and macrovascular complications as the primary causes of death in patients with diabetes. In 1955, sulfonylureas became the first oral medications developed and marketed for the treatment of diabetes. However, testing urine for the presence of sugar was still used as a crude means by which therapeutic decisions could be rationalized. The Ames glucometer, introduced in 1970, provided patients with the first tool for performing self-monitoring of blood glucose (SMBG), which has since become an important component of diabetes management. Metformin was approved by the U.S. Food and Drug Administration (FDA) in 1995. In 2010, more than 48 million prescriptions for generic metformin were filled in the United States alone (IMS Institute for Healthcare Informatics, 2011).

In 1993, the Diabetes Control and Complications Trial (DCCT) demonstrated that intensive glycemic control (i.e., keeping blood glucose levels as close as possible to the normal range) reduces the incidence and progression of microvascular complications (e.g., retinopathy, nephropathy, and neuropathy) in T1DM (DCCT Research Group, 1993). Whether the same held true in T2DM remained uncertain until 1998, when the U.K. Prospective Diabetes Study (UKPDS) established that intensively lowering blood glucose levels reduces microvascular complications in T2DM as well (UKPDS Study Group, 1998). However, these and other landmark long-term, randomized controlled trials (RCTs) have consistently demonstrated that individuals whose diabetes is intensively managed have a higher risk of hypoglycemia; weight gain; and, in some cases, all-cause mortality than their peers who are treated to a more relaxed or conventional glycemic target (Action to Control Cardiovascular Risk in Diabetes [ACCORD] Study Group, 2008, The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE] Collaborative Group, 2008, DCCT Research Group, 1993; Duckworth et al., 2009; UKPDS Study Group, 1998).

Based on the findings of the DCCT and UKPDS, the ADA recommends an A1C target of 6.5% to 7% for most healthy patients in the United States (ADA, 2013b). However, rather than focusing on a specific glycemic target, care should be customized based on factors such as the patient's age, disease duration, hypoglycemia risk, presence or absence of significant comorbidities, expected longevity, and capability for and attitudes regarding diabetes self-management (Ismail-Beigi et al., 2011). Metabolic targets for lipids and blood pressure should also be customized. Following a healthy lifestyle, including a healthy eating plan, adequate physical activity, modest weight reduction (8-10 lb), and smoking cessation, is crucial for reducing the risk of long-term complications. Finally, SMBG should be incorporated into every patient's daily routine as a means of identifying glycemic variability, predicting hypoglycemia, and evaluating immediate responses to therapeutic interventions.

The recent guideline modifications regarding individualizing metabolic targets notwithstanding, American medicine is achieving a historic level of success in treating this chronic progressive illness. Ninety percent of all patients with diabetes are managed in the primary care setting (Unger, 2012c). Some critics argue that practitioners are failing to treat patients successfully to their metabolic targets; apparently, these naysayers do not understand the importance of positive trending. Recently published data from the National Health and Nutrition Examination Survey (NHANES) suggested that, in 2010, 18.8% of all patients with diabetes successfully achieved an A1C of less than 7%, a blood pressure less than 130/80 mm Hg, and a low-density lipoprotein (LDL) cholesterol level less than 100 mg/dL compared with only 1.7% of surveyed individuals with diabetes from 1988 to 1994 (Stark Casagrande, et al., 2013).

American medicine is changing. Our treatments for diabetes, hypertension, and hyperlipidemia have improved. These improvements in the management of diabetes and related disorders may be attributed in large part to the primary care providers who care for the increasingly high numbers of patients exposed to prolonged glycemic burden, as well as to patients' desire to become more active participants in their own diabetes care. The renewed emphasis on individualized, patient-centered diabetes care may further expand our success in this area in the near future.

Prediabetes: A Treatable Precursor of Type 2 Diabetes

Diabetes affects 25.8 million Americans (18.8 million have been diagnosed with diabetes, and an estimated 7 million remain undiagnosed). Based on NHANES data obtained between 2005 and 2008, 35% of U.S. adults 20 years of age or older and 50% of individuals 65 years of age and older meet the diagnostic criteria for prediabetes. In 2010, 79 million Americans were estimated to have prediabetes. In 2011, an estimated 280 million people were estimated to have *prediabetes* worldwide (ADA, 2011b). By 2030, the

Table 34-1 Diagnosing Prediabetes and Diabetes

Parameter	Euglycemia	Prediabetes	Diabetes
Fasting glucose (mg/dL)	<100	100-125 (impaired fasting glucose)	>126
2-hour postprandial glucose (mg/dL)	<140	140-199 (impaired glucose tolerance)	>200
A1C (%)	<5.7	5.7-6.4	>6.5

Data from American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 36(suppl 1):S67-S74, 2013.

International Diabetes Federation predicts that this number will increase to 400 million as westernization and obesity push into Asia, Africa, and South America (Unger and Moriarty, 2008).

The costs of caring for patients with diabetes will continue to rise. Annual health care costs in the United States for a person without diabetes are $5615. Diabetes inflicts a 2.3-fold increase in annual costs of care, raising this figure to $12,195. In 2012, diabetes cost $245 billion in health care expenditures, an increase of 41% since 2007. Astonishingly, diabetes care now accounts for nearly 30% of the total Medicare budget. Thus, screening and implementing preventive strategies for prediabetes warrant political, medical, and bioethical consideration (ADA, 2013a).

Diabetes is a chronic, progressive disorder that, over the course of time, exposes patients to a prolonged, excessive glycemic burden, which activates pathways favoring oxidative stress and endothelial cell dysfunction. Complication pathways are propagated, resulting in micro- and macrovascular disease. Given the physical, emotional, and financial consequences associated with diabetes, screening high-risk patients could identify those with an intermediate form of dysglycemia who are likely to progress to clinical diabetes. The diagnostic criteria for prediabetes and diabetes are shown in Table 34-1.

Between 6% and 10% of patients with impaired glucose tolerance (IGT) progress to clinical diabetes each year, but up to 65% of individuals with both impaired fasting glucose (IFG) and IGT progress to clinical diabetes annually (Garber et al., 2008). Progression rates of IFG or IGT to diabetes vary according to degrees of initial hyperglycemia, racial and ethnic backgrounds, and environmental influences. The higher the glucose values, the greater the risk of progression to diabetes and diabetes complications. Primary care physicians are trained not only in managing patients within effective chronic disease-state models but also in identifying patients who are likely to develop diseases such as hypertension, diabetes, obesity, and cancer. High-risk individuals, after they have been identified (Table 34-2), should be screened for prediabetes and diabetes.

A1C has also been shown in prospective studies to predict progression to clinical diabetes. Zhang et al. (2010) noted that whereas individuals with a screening A1C at baseline of between 5.5% and 6% had a 5-year progression rate of 9% to 25%, those with an A1C of 6% to 6.5% progressed over 5 years at a rate of 25% to 50%.

Diagnostic tests for prediabetes and diabetes should be repeated to rule out laboratory error unless the diagnosis is unequivocal. A screened symptomatic patient with an A1C of 7.9% and a random blood glucose of 265 mg/dL can simply be treated for diabetes. However, a patient with a screening A1C of 6.2% with a euglycemic 2-hour post–glucose challenge value should be rescreened. Preferably, the same test should be repeated for confirmation. If the initial A1C is 6.4% with a secondary measurement performed 2 months later of 6.3%, the diagnosis of prediabetes is confirmed. One can also make the diagnosis of prediabetes if the results of two different tests such as the A1C and the 2-hour post–glucose challenge are higher than diagnostic thresholds.

Table 34-2 Screening Patients at High Risk for Developing Prediabetes

Patients at Risk for Developing Prediabetes	Patients to Target for Prediabetes Screening
History of PCOS	Family history positive for diabetes
History of GDM	History of cardiovascular disease
Children of parents with T2DM	Obesity
Patients with abdominal obesity	Sedentary lifestyle
	Nonwhite ancestry
	Previous history of IGT or IFG
	History of hypertension
	History of elevated triglycerides, low HDL cholesterol, or both
	History of GDM
	History of PCOS
	Delivery of a baby weighing >9 lb
	Patients with schizophrenia or bipolar disorder

GDM, Gestational diabetes mellitus; *HDL,* high-density lipoprotein; *IFG,* impaired fasting glucose; *IGT,* impaired glucose tolerance; *PCOS,* polycystic ovary syndrome; *T2DM,* type 2 diabetes mellitus.
Data from Garber AJ, Handelsman Y, Einhorn D, et al. Diagnosis and management of prediabetes in the continuum of hyperglycemia: when do the risk of diabetes begin? A consensus statement from the American College of Endocrinology and the American Association of Clinical Endocrinologists. *Endocr Pract.* 14:933-945, 2008.

A1C can be useful as a screening tool for patients who present to the emergency department for management of an acute illness. An A1C greater than 5.7% performed in the acute-care setting has a sensitivity of 54.8% and a specificity of 71.3% for detecting prediabetes. An A1C of 6% has a sensitivity of 76.9% and a specificity of 87.3% for diagnosing diabetes in the acute-care setting (Silverman et al., 2011).

To prevent progression to clinical diabetes, the ADA recommends moderate exercise, weight loss (7%-10% of baseline weight in obese individuals), consideration of metformin (in patients with a body mass index [BMI] >35 kg/m^2; age younger than 60 years; or, in women, a history of GDM) (ADA, 2013b). Modifiable cardiovascular disease (CVD) risk factors must also be addressed, including smoking cessation, targeting blood pressure to less than 140/90 mm Hg, and targeting LDL cholesterol to less than 100 mg/dL. A recent study suggested that a single period of moderate

exercise expending 350 kcal of energy can improve insulin sensitivity for obese patients into the following day (Newsom et al., 2013). In the Nurses' Health Study, whereas each 2-hour increment spent watching television daily was associated with a 14% increased risk of developing T2DM, a similar increment spent standing or walking was associated with a 12% risk reduction (Hu et al., 2011).

The relationship among environmental factors, the increased risk of obesity, and a reduction in desire to increase physical activity is well established. Unfortunately, the acute medical models fail to address meaningful and effective strategies that may prevent or reverse the diabetes epidemic. Proactive public health initiatives designed to educate parents and children about the importance of healthy lifestyle choices may be our best hope for minimizing the nuclear burden of the looming health care costs associated with chronic hyperglycemia.

Zhang et al. (2003) suggested that screening obese patients for prediabetes is cost effective. Screening studies cost less than $200 per case. Patients who screen positive for prediabetes can initiate low-cost lifestyle interventions and metformin, if necessary. These noninvasive therapies will result in a savings of greater than $8000 per quality-adjusted life year gained for screened individuals.

Weight reduction and physical activity can improve insulin-mediated glucose disposal, reduce postprandial hyperglycemia, delay pancreatic β-cell death, and slow the progression of glucose intolerance to clinical T2DM.

The Diabetes Prevention Program (DPP) was the most comprehensive clinical trial to date evaluating the importance of lifestyle modification as a deterrent to diabetes in high-risk patients (Knowler et al., 2002). A total of 3234 overweight subjects with prediabetes were randomized to one of three cohorts. The intensive lifestyle intervention (ILI) group received intensive instruction in diet, physical activity, and behavioral modification. The patients assigned to this group were counseled to reduce their fat and calorie consumption and to exercise for 150 minutes per week and were targeted to lose 7% of their baseline weight. Subjects in the ILI group reduced their risk of progression to diabetes by 58% over 4 years. The second group used metformin, 850 mg twice daily, and received information regarding lifestyle intervention but no intensive counseling. Their risk of progression to clinical diabetes was reduced by 31%. The control group was given a placebo in place of metformin and attended classes related to lifestyle intervention. About 5% of the lifestyle intervention group developed diabetes each year during the study period compared with 11% of those in the placebo group. A follow-up to the DPP showed that preservation of β-cell function and delay of progression to diabetes in high-risk individuals can persist for at least 10 years with lifestyle intervention or metformin (DPP Research Group, 2009).

The FDA has not approved any pharmacotherapeutic agents for the treatment of prediabetes. However, several therapies have proven to be effective at delaying or preventing the progression of prediabetes to diabetes. Compared with placebo, acarbose has been shown to reduce progression of prediabetes to T2DM by 25% over a 3.3-year period regardless of age, sex, or BMI (Chiasson et al., 2003).

Pioglitazone reduced the risk of conversion to diabetes in patients with isolated IGT or with combined IFG and IGT in both men and women, as well as in all age and weight groups compared with placebo (DeFronzo et al., 2011). Unfortunately, the mean weight gain in pioglitazone-treated patients was 3.6 kg. Thus, one might argue that pioglitazone may be a strong candidate as a pharmacologic intervention for prediabetes. However, use of pioglitazone in this patient population will likely result in weight gain.

The ORIGIN Trial (Outcome Reduction with Initial Glargine Intervention) was a 6-year RCT designed to assess the effects of treatment with insulin glargine compared with standard care on cardiovascular outcomes in more than 12,500 subjects worldwide. Study participants had either prediabetes or early T2DM, as well as a high cardiovascular risk profile. A total of 6264 patients were randomized to receive glargine titrated to achieve fasting normoglycemia. Glargine achieved the targeted long-term glycemic control (median fasting glucose of 93.6 mg/dL and A1C of 6.2%) over 6.2 years without increasing the overall incidence of cancer or heart disease. In addition, glargine delayed the progression from prediabetes to T2DM by 28%. However, patients randomized to the glargine group experienced nearly three times the frequency of hypoglycemia events compared with those in the standard cohort and gained on average 3.5 lb over the course of the study (Gerstein et al., 2012).

Recommended treatment strategies for managing prediabetes vary depending on the particular published guidelines consulted and are summarized in Table 34-3.

In summary, patients who are at high risk for diabetes should be screened for prediabetes and clinical diabetes using a fasting blood glucose, 2-hour post-glucose challenge, or A1C test (assuming patients are not pregnant). Unless a patient has symptoms strongly suggestive of diabetes (e.g., thirst, weight loss, blurred vision, paresthesias, and fatigue) in association with significantly abnormal screening laboratory values, a diagnosis of abnormal glucose tolerance should be confirmed with repeat testing.

For individuals who are diagnosed with prediabetes (IFG or IGT), adoption of healthy lifestyle choices with the goal of restoring normal glucose regulation becomes the key to preventing disease progression to T2DM. Every 1 kg of weight lost is associated with a 16% reduction in the risk of progression to diabetes. Physical activity improves peripheral insulin resistance and enhances weight loss.

Patients also should be instructed to monitor their blood glucose levels. One common recommendation is to perform 7-point SMBG (before and after each meal and at bedtime) for 3 successive days before each clinic appointment. This will allow the clinician to gauge changes in fasting and postabsorptive glucose values that require attentive intervention.

The American Association of Clinical Endocrinologists (AACE) recommends initiating off-label use of metformin in patients likely to progress to clinical diabetes whose A1C level is greater than 6.0% (Garber et al., 2008). The pharmacologic goal of prediabetes management should be directed toward pancreatic β-cell preservation. Patients who have prediabetes have lost 80% of their β-cell function and are considered to be maximally insulin resistant (Gastaldelli et al., 2004).

Ambitious screening of high-risk patients and encouragement of healthy lifestyle principles by primary care

Table 34-3 Management and Prevention of Type 2 Diabetes Mellitus in High-Risk Individuals

Published Guidelines	Clinical Recommendations for the Management of Prediabetes
American Diabetes Association	Refer to effective ongoing support program targeting a weight loss of 7% from baseline At least 150 min/wk of moderate physical activity such as walking Consider metformin if A1C increases above the threshold of 6% despite lifestyle intervention Monitor annually for progression to clinical diabetes
American Association of Clinical Endocrinologists	Lifestyle intervention strategies, including weight reduction of 5% to 10% from baseline with long-term maintenance Moderate-intensity exercise program for 30 to 60 min/day at least 5 days/wk Dietary recommendations: lower sodium intake, avoidance of excessive alcohol, caloric restriction, increased fiber intake, possible limitation on carbohydrate intake Initiation of metformin or acarbose for "low-risk" patients or pioglitazone for "high-risk" patients or for those in whom lower-risk therapies have not succeeded Incretin therapies may also prove effective in β-cell preservation No targeted A1C is recommended Use statins to achieve an LDL cholesterol level <100 mg/dL, non-HDL cholesterol <130 mg/dL, and/or apolipoprotein B ≤90 mg/dL) Target blood pressure of <130/80 mm Hg Antiplatelet therapy (low-dose aspirin) for all patients with prediabetes for whom there is no identified excess risk for GI, intracranial, or other hemorrhagic condition

GI, Gastrointestinal; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein.
Adapted with permission from Unger J. *Diabetes management in primary care*. 2nd ed. Philadelphia: Lippincott, Williams and Wilkins; 2012.

physicians will reduce the number of individuals who ultimately progress to clinical diabetes and suffer the consequences of a chronic hyperglycemia burden.

Type 2 Diabetes Mellitus

PATHOGENESIS

The Genome-Wide Association study has detected 18 polymorphisms (genetic variations) that may increase a person's likelihood of developing T2DM (Hamman, 1992). Over time and under the influence of environmental triggers, the activation of these alleles distorts the homeostatic control of normal glycemia (Unger, 2012d). Several of the recently described activators of prediabetes and T2DM pathogenesis that may be of particular interest to family physicians are discussed in Table 34-4. Other environmental triggers include low levels of vitamin D; obesity; high-fat diets; lack of physical activity; concurrent illnesses; and use of certain prescription medications, which may induce treatment-emergent diabetes.

Genetically susceptible individuals may possess polymorphisms (alterations in the normal DNA sequencing that form a typical allele) that favor reduction in satiety, increased appetite, reduced energy expenditure, and increased intraabdominal fat accumulation. These individuals will become obese, which will induce physiological stress and overproduction of insulin by their pancreatic β cells. Over time, genetic coding will begin the process of programmed β-cell death (apoptosis). The San Antonio Metabolism Study demonstrated that patients with prediabetes who have 2-hour postprandial glucose levels of 140 to 180 mg/dL have effectively lost 80% of their β-cell function and are maximally insulin resistant. Additionally, 18% of patients with prediabetes are already diagnosed with diabetic retinopathy (Gastaldelli et al., 2004). Thus, the dreaded long-term microvascular (i.e., retinopathy, neuropathy, and nephropathy) and macrovascular (i.e., coronary heart disease, peripheral vascular disease, and stroke) complications are already in the progressive stages long before these patients progress to T2DM.

MAINTENANCE OF NORMAL GLUCOSE HOMEOSTASIS AND DIABETES PATHOGENESIS

Glucose homeostasis is rigidly maintained within the range of 85 to 140 mg/dL via the interaction of multiple hormones (i.e., insulin, glucagon, amylin, leptin, resistin, glucagon-like peptide 1 [GLP-1], glucose-dependent insulinotropic polypeptide [GIP], adiponectin, growth hormone, cortisol, and somatastatin). Insulin modulates the metabolism of fat and protein while regulating intracellular transport of glucose. Insulin also regulates hepatic glucose production and peripheral glucose uptake and disposal by skeletal muscles and limits lipolysis. The body stores approximately 450 g of glucose, which is used as an energy source for the brain, skeletal muscles, and cellular metabolism. The brain requires 125 g of glucose daily. Another 125 g of glucose is used by the rest of the body. Daily intake of 180 g of dietary glucose and 70 g of glucose from gluconeogenesis (via the kidneys and liver) replenishes the body's glucose stores (Unger, 2012a).

A decrement in plasma glucose of as little as 20 mg/dL (i.e., from 90 to 70 mg/dL) will suppress β-cell insulin release while triggering the release of counterregulatory hormones (i.e., glucagon, catecholamines, cortisol, and growth hormone) (Gerich, 1988). Likewise, a 10-mg/dL increase in plasma glucose will stimulate insulin secretion and mitigate glucagon release by the pancreatic α cells (Shrayyef and Gerich, 2010).

Postabsorptive endogenous glucose release is maintained by hepatic glycogenolysis (the breakdown of glycogen, accounting for 50% of the total basal glucose) and hepatic gluconeogenesis (the formation of glucose from noncarbohydrate molecules such as amino acids and lactic acidosis, accounting for 30% of the body's basal glucose). Renal gluconeogenesis provides an additional 20% of the body's total endogenous energy stores. This "basal glucose" prevents hypoglycemia while supplying sufficient energy

Table 34-4 Environmental Activators of Type 2 Diabetes Mellitus

Environmental Activator	Suspected Mechanism Leading to Induction of Type 2 Diabetes Mellitus
Advanced age	Aging-related alterations of DNA methylation can affect cell signaling and gene transcription. This may upregulate a state of chronic inflammation in older individuals.
Late-morning rising and large caloric intake at dinner (late chronotype)	Late bedtimes and late-morning rising are associated with skipping breakfast and shifting more calories consumed to later in the day. This increases the risk of obesity and diabetes.
Sleep disorders (e.g., obstructive sleep apnea, defective REM sleep, shift work–related, insomnia, and restless leg syndrome)	Circadian misalignment affects sleep architecture as well as glucose–insulin metabolism, substrate oxidation, homeostasis model assessment of insulin resistance index, leptin concentrations, and hypothalamic–pituitary–adrenal axis activity. Depression is common in people with sleep disorders and can also increase diabetes risk.
Mental illness	Patients with major depression, bipolar disorder, or schizophrenia tend to smoke, be physically inactive and overweight, and have increased levels of C-reactive protein (favoring an inflammatory state). Low levels of tissue plasminogen activator in patients with schizophrenia may affect signaling within dopamine neurotransmitters, affecting insulin resistance and promoting diabetes.
Exposure to second-hand smoke	Women exposed to second-hand smoke from at least one parent have been found to have an 18% higher rate of diabetes than nonexposed women. Smoking causes adipocyte hypertrophy, insulin resistance, leptin resistance, and chronic pancreatic inflammation.
History of physical or sexual abuse	Results of the Nurses' Health Study II indicate the following associations: Physical abuse: ■ Moderate: 26% higher diabetes risk in adults ■ Severe: 54% higher diabetes risk in adults Forced sexual activity before adulthood: ■ 1 occasion: 34% higher diabetes risk in adults ■ >1 occasion: 69% higher diabetes risk in adults
Chemical exposure	In patients with a genetic predisposition to the development of diabetes, 10 chemicals have been determined to activate alleles that, in turn, favor the onset of β-cell apoptosis. Chemicals that have the greatest propensity toward β-cell destruction include arsenic, dioxin (a contaminant chemical in Agent Orange), hexachlorobenzene (a banned fungal chemical for agriculture), and perfluorooctanoic acid (a chemical found in Teflon, which is known to be toxic in animals and is found in the blood of 98% of the U.S. population).
Early menarche	Menarche occurring between the ages of 8 and 11 years may increase T2DM risk by up to 70%. Early menarche is associated with obesity and insulin resistance.

REM, Rapid eye movement; *T2DM,* type 2 diabetes mellitus.
References: Audouze et al., 2013; Elks et al., 2013; Gonnissen et al.., 2013; Hoirisch-Clapauch and Nardi, 2013; Johansson et al., 2013; Lajous M et al., 2013; López-Otín et al., 2013; Pouwer et al., 2013; Reutrakul et al., 2013; and Rich-Edwards et al., 2010.

sources for the brain in the fasting state (Gerich et al., 2001). As noted earlier, ingested carbohydrates provide an exogenous source of glucose for the body's energy needs.

Intracellular transport of glucose occurs within skeletal muscles and adipose tissue as endogenous insulin binds to membrane-bound receptors. Glucose transporter type 4 (GLUT4) actively transports glucose intracellularly for storage as glycogen or in adipose tissue as fat.

The gastrointestinal (GI) tract participates in glucose homeostasis by permitting glucose entry to the body during digestion. Approximately 60% of the insulin response to an oral glucose load is prompted by the potentiating effect of two gut-derived incretin hormones. GLP-1, secreted by L cells, helps regulate the rate of glucose appearance by inhibiting glucagon secretion and hepatic glucose production, regulating gastric emptying, and reducing food intake by postulated centrally mediated mechanisms. GIP is secreted by the K cells of the proximal duodenum in response to glucose stimulation enhanced by fat and promotes triglyceride storage in adipose cells.

The levels of both GLP-1 and GIP increase within minutes of eating, probably as a result of a combination of endocrine and neural signals that stimulate incretin release before digested food comes into contact with the L cells of the small bowel and colon. Plasma levels of GLP-1 are low (5-10 pmol/L) in the fasting state and increase rapidly after eating, reaching 15 to 50 pmol/L. Circulating levels of both GLP-1 and GIP decrease rapidly because of enzymatic inactivation via dipeptidyl peptidase-4 (DPP-4) and renal clearance. Approximately two thirds of the insulin response to an oral glucose load results from the potentiating effect of gut-derived incretin hormones.

The pancreas regulates glucose homeostasis by secreting insulin from centrally positioned β cells and glucagon from α cells located on the periphery of the pancreatic islet. Insulin is secreted in response to high plasma glucose levels and GLP-1 stimulation after nutrient intake.

Insulin is normally secreted into the portal circulation in two phases. In the fasting state, basal insulin is secreted at the approximate rate of 1 unit/hr to minimize hepatic glucose production (Kruszynska et al., 1987). Basal insulin also limits lipolysis and excess flux of free fatty acids (FFAs) to the liver, which can result in a state of postabsorptive insulin resistance. The circulating glucose levels are maintained at a level that allows for the extraction of this energy source by obligate glucose consumers such as the central nervous system. Basal insulinopenia (in T1DM) stimulates hormone-sensitive lipase and FFA release from fat stores, which, in turn, triggers hepatic production and release of ketone bodies, leading to ketogenesis and DKA.

The second-phase postprandial glucose peak occurs between 1 and 2 hours after a meal, with a mean peak time of 75 minutes (Slama et al., 2006). Eating prompts a five- to 10-fold increase in prandial insulin release from pancreatic

β cells in euglycemic individuals. The meal-stimulated insulin response is triggered by a rise in plasma glucose and FFA concentrations, as well as neuroendocrine-augmented release of incretin hormones GIP and GLP-1. At basal insulin levels of 5 to 10 microunits/mL, hepatic glucose production and lipolysis (FFA release) are suppressed, which effectively counteracts the hyperglycemic effects of glucagon. Proximal uptake of glucose within skeletal muscles is not effective. As postabsorptive insulin levels exceed 40 to 50 microunits/mL, hepatic glucose suppression becomes optimally suppressed (Shrayyef and Gerich, 2010). This postabsorptive state may last between 4 and 6 hours and is dependent on the food content of each meal. High-fat meals such as pizza prolong the postabsorbtive state (Sheard et al., 2004).

The liver performs two different functions, depending on the level of circulating insulin. In the presence of low levels of insulin (≤25 mU/mL; e.g., in the fasting state), glucose is derived from glycogenolysis and gluconeogenesis to maintain euglycemia (Consoli, 1987). As circulating insulin levels rise, glucose is stored in the liver as glycogen and released into the plasma in response to hypoglycemia. After an overnight fast, the liver of a euglycemic individual produces glucose at a rate of approximately 2 mg/kg/min. Interestingly, in T2DM, despite a threefold increase in circulating plasma insulin levels, the liver will secrete an additional 25 to 30 g of glucose nightly into the plasma. Thus, the primary defect in T2DM appears to be related to peripheral glucose disposal caused by defective skeletal muscle transport rather than excessive hepatic glucose production (Unger, 2012A).

Amylin is a peptide hormone that is co-secreted from pancreatic β cells with insulin and is thus deficient in patients with diabetes. Amylin inhibits glucagon secretion, delays gastric emptying, and acts to increase satiety. Amylin also suppresses postprandial triglyceride concentrations and is known to reduce markers of oxidative stress and endothelial cell dysfunction (Unger, 2008b).

Although FFAs are the primary fuel for most organs, glucose is the obligate energy source of the brain under most physiological conditions. Glucose transport across the blood–brain barrier is more efficient than FFA absorption. During a prolonged fast, FFAs and ketone bodies supply the brain with its metabolic requirements (Shrayyef and Gerich, 2010). Lipolysis increases plasma levels of FFAs, which augment insulin resistance at multiple levels. The rise in FFAs impairs both the first- and second-phase insulin response in genetically predisposed individuals (DeFronzo, 2009). This portends to glucotoxicity occurring with each meal. Chronic exposure to elevated plasma glucose favors β-cell apoptosis (cell death). Hepatic glucose production is also accelerated by a rise in FFAs. Additionally, FFAs competitively bind to insulin receptors on myocytes, after which the GLUT4 transport mechanism is blocked from carrying glucose as an energy source from plasma into cells (DeFronzo, 2009).

Intracellular signaling occurs between the β and α cells such that glucose levels are tightly regulated, minimizing the likelihood of postprandial hypoglycemia. In the presence of decreasing plasma glucose levels, the α cells will signal the β cells to cease insulin production and secretion as glucagon levels rise. The secretion of glucagon results in hepatic gluconeogenesis and a return to euglycemia. As β cell function and mass deteriorates, the neurologic pathways of communication between the α and β cells are disrupted, resulting in excess glucagon production. Clinically, patients experience elevations in fasting and postabsorptive glucose levels.

Table 34-5 Regulators of Normal Glucose Homeostasis

Regulating Component	Glucose Production	Glucose Disposal	Lipolysis
Insulin	↓	↑	↓
Glucagon	↑	—	—
Epinephrine	↑	↓	↑
Cortisol	↑	↓	↑
Growth hormone	↑	↓	↑
FFAs	↑	↓	—
Amylin	—	↓	—*

*Free fatty acids (FFAs) may stimulate release of insulin and amylin.

The role of the kidneys in maintaining normoglycemia through the filtration and reabsorption of glucose and gluconeogenesis is well established. Each day, 180 L of plasma filters through the kidneys, translating into a filtration load of approximately 180 g of glucose. Ninety percent of renal glucose reabsorption occurs within the proximal glomeruli tubules, where sodium–glucose co-transporter 2 (SGLT2) is present. Ten percent of circulating glucose is reabsorbed in the distal tubules via sodium–glucose co-transporter 1 (SGLT1). SGLT1 is also expressed in the gut and is responsible for absorption of both dietary glucose and galactose. The glucose transport mechanism becomes saturated when plasma glucose levels exceed 180 to 190 mmol/L. Beyond the point of transporter saturation, any additional glucose is detected as glycosuria (DeFronzo et al., 2012). The key hormonal and metabolic regulators of normal glucose homeostasis are shown in Table 34-5.

Insulin acts as a growth factor in the brain and supports neuronal repair, dendritic sprouting and synaptogenesis, and protection from oxidative stress. The increased risk of Alzheimer disease, Parkinson disease, and stroke in people with T2DM suggests that shared mechanisms or pathways of cell death, possibly related to insulin dysregulation, may underlie all of these disorders. Although the disease anatomy varies with each disorder, a wide range of genetic and environmental factors triggers activation of similar biochemical pathways in all of them, suggesting a complex network of biochemical events that feed into a final common path toward cellular dysfunction and death (Rasool et al., 2013).

Patients with T2DM exhibit multiple abnormalities in glucose homeostasis, including impaired first- and second-phase insulin secretion; inappropriately timed and excessive glucagon secretion; increased hepatic glucose production despite elevations in endogenous plasma insulin levels; reduced peripheral uptake of glucose within skeletal muscle cells; loss of central neural protection promoting alterations in satiety and weight gain; an overexpression of SGLT2 within the renal proximal tubules, subsequently increasing plasma reabsorption of glucose and promoting insulin resistance; amplified lipolysis, resulting in β cell apoptosis; and loss of the meal-triggered insulin response, which may

Table 34-6 Summary of Pathological Deficits Associated with Type 2 Diabetes Mellitus

Target Organ/Tissue	Physiological Defects	Glycemic Effects
Pancreatic β cells	Loss of first-phase insulin secretion Delayed second-phase insulin secretion Loss of amylin secretion	Glucose toxicity results in β-cell apoptosis.
Pancreatic α cells	α-Cell hypertrophy Loss of α- and β-cell signaling results in loss of appropriate and timely counterregulation; patients are more likely to develop hypoglycemia awareness autonomic failure over time. Exaggerated, paradoxical, and untimely secretion of glucagon during both the fasting and postprandial states	Hyperglucagonemia results in glucose toxicity, β-cell destruction, and excessive hepatic glucose production. Patients experience an increase in fasting and postprandial glucose levels; this increases their A1C. Insulin resistance is exacerbated.
Hepatocytes	Excessive hepatic glucose production despite initial elevations in circulating plasma insulin levels The liver excretes >25 g/day of extra glucose into the plasma	Increases insulin resistance Increases gluconeogenesis and glycogenolysis
Myocytes	Impaired uptake and intracellular utilization of glucose	Increases peripheral insulin resistance Increases fasting and postabsorptive glucose levels Marked deficiency in peripheral glucose utilization is the most significant defect observed in insulin resistance.
Gut	Reduction in secretion of GLP-1 and GIP by the intestines in response to oral glucose stimulation When GLP-1 is secreted, ≈80% of the gut hormone is immediately deactivated by DPP-4; reduced levels of GLP-1 result in proportionally lower amounts of GLP-1 being expressed at pancreatic β-cell receptors. GLP-1 resistance at target tissue site Amylin levels are reduced within pancreatic islets; amylin and insulin are co-secreted in a glucose-dependent manner.	Alters gastric emptying Causes weight gain Increases fasting and postprandial glucose levels Reduces sense of satiety Causes loss of neuroprotection against Alzheimer disease and Parkinson disease Reduction in amylin accelerates gastric emptying and impairs satiety. The overall effect is a rise in postprandial glucose values.
Adipose tissue	Increased lipolysis in response to a reduction in circulating endogenous insulin	β-cell destruction Increases FFAs Increases hepatic glucose production because the liver is unable to store glycogen Impairs GLUT4 transport of glucose into muscle, exacerbating peripheral insulin resistance
Brain	Loss of neuroprotection	Increases appetite Favors obesity Increases oxidative stress Insulin resistance appears to be associated with Alzheimer disease and Parkinson disease.
Kidneys	Increased expression of SGLT2 in the proximal glomerular tubules Daily renal filtered glucose threshold increases from 180 to 240 g/day.	90% of filtered glucose is absorbed via SGLT2 in the proximal tubules, and 10% is absorbed by SGLT1 in the distal tubules. SGLT1 is also expressed in the gut, where daily dietary glucose absorption of 180 g occurs. If the renal glucose threshold of the SGLT2 transport mechanism is surpassed, glycosuria occurs. In T2DM, the threshold is increased from 180 to 240 g/day, which results in an increased renal absorption of glucose regardless of the patient's state of chronic hyperglycemia. Excessive reabsorption of glucose from the kidneys exacerbates insulin resistance.

DPP-4, Dipeptidyl peptidase-4; *FFA,* free fatty acid; *GIP,* glucose-dependent insulinotropic polypeptide; *GLP-1,* glucagon-like peptide 1; *GLUT4,* glucose transporter type 4; *SGLT2,* sodium–glucose co-transporter 2; *T2DM,* type 2 diabetes mellitus.

Data from DeFronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 58:773-795, 2009.

maintain weight and euglycemia for years. Table 34-6 summarizes the common pathogenic pathways related to T2DM.

The pathogenesis of T2DM is multifactorial. Genetically or environmentally challenged individuals begin the transformation from euglycemia to clinically apparent T2DM as their skeletal muscles and hepatocytes exhibit early evidence of insulin resistance. Initially, pancreatic β cells attempt to compensate for IGT by overproducing insulin. Obesity plays a major role in the progression of prediabetes to T2DM. Compared with lean individuals, overweight euglycemic subjects appear to require a longer time to achieve satiety, and the magnitude of their appetite suppression also reduced (Matsuda, 1999). Thus, obesity tends to become self-promoting. As meal portions increase, so does the secretion of GLP-1, resulting in β-cell hypertrophy.

Few individuals can maintain hypersecretion of insulin for a prolonged period of time. Patients who have primary relatives with T2DM will lose their acute, first-phase insulin response to a glucose stimulus and experience a delay in the initiation of their second-phase response. IGT will now become apparent as patients progress into a state of prediabetes. Over time, other metabolic defects appear, which tend to aggravate the existing state of hyperglycemia. As endogenous insulin levels decline, lipolysis is accelerated because insulin action normally stabilizes fat cells. Lipolysis further aggravates the first-phase insulin response, promotes

Table 34-7 Factors Promoting Patients' Adherence to Their Diabetes Management Regimen

Higher socioeconomic status and level of education
Resolution of comorbid mental illness symptomatology
Spousal, familial, and communal support
Satisfaction with doctor–patient relationship
Availability of and support from a diabetes health care team
Appointment reminder cards, reminder phone calls regarding upcoming appointments, minimal clinic waiting room delays, and emphasis on the positive aspects of patient's diabetes self-management efforts rather than on patient's failures or oversights
Simplified treatment regimens
Particular aspect of the regimen; patient adherence to medication regimens surpasses their adherence to lifestyle or behavioral recommendations
Co-management of "complex" patients with a mental health professional

Reprinted with permission from Unger J. *Diabetes management in primary care*. 2nd ed. Philadelphia: Lippincott, Williams and Wilkins; 2012.

Table 34-8 Medical Nutrition Therapy Recommendations for Patients with Diabetes

Patients with diabetes should receive customized MNT recommendations from a registered dietitian who is familiar with the components of diabetes nutritional interventions.
Portion control and healthy food choices are suitable options for patients with literacy and numeracy concerns. Older adults may also benefit from this simplified approach to meal planning.
Reducing food intake and increasing energy expenditure is recommended to promote weight loss in obese adult patients with T2DM.
Modest weight loss may result in improvement in glycemia, blood pressure, and lipids, especially when initiated soon after patients are diagnosed with diabetes. Intensive lifestyle education and management is recommended for newly diagnosed patients with diabetes.
The optimal mix of macronutrients (i.e., carbohydrates, fats, and proteins) in the daily diet should be individualized.
Patients' personal preferences regarding foods and metabolic goals should be considered when discussing eating patterns and meal planning.
Substituting low–glycemic index foods for higher–glycemic index foods may modestly improve glycemic control.
People with diabetes should consume fiber and whole grains in a manner similar to what is recommended to the general public.
People with diabetes should minimize their consumption of sugar-containing beverages.

MNT, Medical nutrition therapy; *T2DM,* type 2 diabetes mellitus.
Data from Evert AB, Boucher JL, Cypress M, et al. Nutrition therapy recommendations for the management of adults with diabetes. *Diabetes Care*. 36:3821-3842, 2013.

glycogen breakdown by hepatocytes, and prevents the peripheral uptake of glucose by skeletal muscle cells.

The complex pathogenesis of diabetes underscores the importance of combining rational polypharmacy designed to target specific metabolic defects with ILIs when managing patients with T2DM.

LIFESTYLE INTERVENTIONS FOR TYPE 2 DIABETES MELLITUS

Lifestyle interventions focusing on both diet and physical activity are clearly beneficial for patients with diabetes. Reducing caloric intake to 1100 kcal/day has been shown to decrease fasting blood glucose levels in obese patients with T2DM and in those with normal glucose tolerance in as few as 4 days (Markovic et al., 1998).

Behavior changes are almost always necessary for patients to adopt and maintain a healthy lifestyle, reduce their long-term risks, and perform daily self-care tasks essential to attaining adequate glycemic control. By some estimates, fewer than 50% of patients with diabetes adhere to recommended lifestyle and behavioral guidelines (Peyrot et al., 2005). Furthermore, adherence is a multidimensional concept in that some patients may comply with their medication regimens while ignoring dietary or physical activity recommendations. Others, who say they "feel just fine," may try to exercise for 2 to 3 hours per day in an attempt to avoid starting medications that are needed to manage their hyperglycemia, hypertension, and hyperlipidemia. In addition, a study of NHANES data collected from patients with T2DM found that 29% of insulin-treated patients, 65% of those taking oral medications, and 80% of those whose diabetes was managed by diet and exercise alone either never performed SMBG—a key component of diabetes self-management—or did so less than once a month (Harris, 2001). Factors that promote patient adherence to their diabetes management regimen are listed in noted in Table 34-7.

New ADA nutrition guidelines published in 2013 focus on overall nutrition and patient preferences rather than any particular dietary prescription (Evert et al., 2013). The "diabetic diet" has been officially replaced with concepts such as "healthful eating patterns" and "individualized eating plans." Clinicians should emphasize personal characteristics and preferences (e.g., patients' tradition, culture, religion, health beliefs, health goals, and financial circumstances) when providing nutrition counseling. In addition, clinicians should refer newly diagnosed patients with diabetes to a registered dietitian to ensure that they receive timely and appropriate medical nutrition therapy (MNT). Highlights of the ADA nutrition recommendations are listed in Table 34-8.

The Look AHEAD study was a 4-year RCT comparing ILI with standard diabetes education and support in 4503 adult patients with T2DM and BMIs of 25 kg/m^2 or greater. The study sought to determine the frequency of remission from T2DM to prediabetes or normoglycemia between the two groups of subjects. Partial or complete remission of diabetes was defined as transition from meeting the criteria for a diagnosis of diabetes to having prediabetic or nondiabetic levels of glycemia (fasting plasma glucose <126 mg/dL and A1C <6.5% with no antihyperglycemic medication). Partial or complete remission was observed in 11.5% (95% confidence interval, 10.1%-12.8%) of the ILI group at 4 years compared with 1.5% to 2.7% of the conventionally managed individuals (P <0.001), thus supporting the importance of early lifestyle intervention after patients are diagnosed with diabetes (Gregg et al., 2012).

Intensive lifestyle intervention also has been considered as a means by which cardiovascular risk may be reduced. Although the Look AHEAD study successfully improved T2DM remission rates when ILI was initiated soon after diagnosis, weight loss and exercise did not translate into a reduction in cardiovascular risk. Weight loss was greater in the intervention group than in the control cohort throughout the study (8.6% vs. 0.7% at 1 year and 6.0% vs. 3.5%

at study end after 9.6 years). The ILI group also demonstrated greater reductions in A1C and greater initial improvements in fitness and cardiovascular risk factors. However, cardiovascular end points occurred in 403 patients in the intervention group and in 418 patients in the control group ($P = 0.51$). Thus, ILI focusing on weight loss did not appear to reduce the rate of cardiovascular events in overweight or obese adults with T2DM (Look AHEAD Research Group, 2013).

Obesity prevalence rates began to increase sharply 30 years ago, and obesity has since emerged as a global public health hazard. Thirty-five percent of the U.S. adult population is obese (BMI ≥30 kg/m^2), and another 35% is classified as overweight (BMI, 25-29.9 kg/m^2) (Flegal et al., 2012). Obesity is associated with disorders such as metabolic syndrome, prediabetes, T2DM, and CVD. Indeed, 80% of patients with T2DM are overweight or obese (National Diabetes Information Clearinghouse, 2013). The third report of the U.S. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults classified T2DM as a coronary heart disease risk equivalent (NCEP Expert Panel, 2002). This classification was based in part on the observation that people with T2DM and no prior myocardial infarction (MI) (mean age, 58 years) were at the same risk as people without diabetes who had a prior MI (mean age, 56 years) for MI (20% and 19%, respectively) and coronary mortality (15% and 16%, respectively) (Haffner et al., 1998).

Therapy for obesity includes lifestyle modification, pharmacologic interventions, and bariatric surgery. The presence and severity of obesity-related complications should be assessed before initiating therapy for overweight patients. Complications related to insulin resistance include hypertension, hyperlipidemia, treatment-resistant diabetes, obstructive sleep apnea, proteinuria, and fatty liver disease. Patients also may have complications related to mechanical or functional disorders, including gastroesophageal reflux, stress incontinence, immobility, and joint pain.

Weight loss medications (i.e., phentermine/topiramate ER, lorcaserin) should be considered for overweight or obese patients with T2DM who fail to achieve moderate weight loss (i.e., ≈10% of their baseline weight) through lifestyle modification (Garvey, 2013). Weight loss drugs can also be used in conjunction with certain oral agents for diabetes (e.g., metformin, SGLT2 inhibitors, and GLP-1 receptor agonists), which are discussed in greater detail in the Long-Term Complications of Diabetes section of this chapter. Patients who fail to improve their metabolic profiles while using FDA-approved weight loss agents may be candidates for bariatric surgery (also known as "metabolic surgery").

Bariatric surgery consists of several well-defined procedures. Restrictive surgeries such as laparoscopic adjustable gastric banding (LAGB) and vertical banded gastroplasty (VBG) reduce the volume of the stomach by 85% to decrease food intake and induce early satiety. VBG is also known as sleeve gastrectomy. LAGB is considered a minimally invasive intervention through which a restrictive band is placed around the upper stomach to partition a small proximal pouch. Initially, these bands were designed for open surgical placement and were not adjustable. However, further refinement has now enabled surgeons to place the adjustable appliance laparoscopically. Malabsorptive procedures such as biliopancreatic diversion (BPD) shorten the small intestine to decrease nutrient absorption. Combined procedures such as the roux-en-Y gastric bypass (RYGB) incorporate both restrictive and malabsorptive elements. RYGB surgery is considered the gold-standard treatment for severe obesity. Both BPD and RYGB alter the secretion of gut hormones that affect satiety. Factors that predict the resolution of T2DM after bariatric surgery are listed in Table 34-9. Table 34-10 lists the benefits of bariatric surgery for patients with T2DM.

Patients who are considering bariatric surgery should be counseled about the risks and benefits of the different types of available procedures. Specific contraindications to bariatric surgery are few and include mental or cognitive impairment that limits patients' ability to understand the procedure and thus precludes informed consent. Very severe coexisting medical conditions such as unstable coronary artery disease or advanced liver disease with portal hypertension may, in some instances, render the risks of surgery unacceptably high. On average, bariatric surgery is associated with a mortality risk in the range of 0.3%. Significant or major complications occur in just over 4% of patients (Flum et al., 2009).

Table 34-9 Preoperative Factors Positively Predicting Diabetes Resolution after Bariatric Surgery in Severely Obese Patients with Type 2 Diabetes Mellitus

Baseline A1C of 6.5% to 7.9% (77% remission rate vs. 50% remission rate for those having a baseline A1C >10%)
Duration of diabetes of ≤5.5 years
Baseline C-peptide >3 ng/mL (suggestive of severe insulin resistance)
Baseline BMI >45 kg/m^2
Significantly elevated basal and 2-hour postprandial insulin levels

BMI, Body mass index.

Data from Schernthaner G, Brix JM, Kopp HP, et al. Cure of type 2 diabetes by metabolic surgery? A critical analysis of the evidence in 2010. *Diabetes Care.* 34(suppl 2):S355-S360, 2011.

Table 34-10 Benefits of Bariatric Surgery in Severely Obese Patients with Type 2 Diabetes Mellitus

Average 1.72 life-years gained in patients with a history of diabetes for <5 years before surgery
Patients with a BMI of 30-34 kg/m$_2$ have the most cost-effective outcomes over time
Cost-effectiveness ratio of $7,000 to $12,000 per quality-adjusted life year gained
Cost savings greatest in patients 65 to 74 years of age who have had diabetes for <5 years
Bariatric surgery resulted in a remission rate of ≈40% to 80%
(After bariatric surgery, the likelihood of diabetes relapse is 8% annually.)
Systolic blood pressure reduced 11.25% during the first 2 years followed by an additional 1.4% reduction until year 10; no further improvement in blood pressure observed thereafter
Total cholesterol reduced 16.1% during the first 2 years followed by a 1.2% reduction each year thereafter until year 10
HDL cholesterol improves 10% during the first 2 years and then decreases by 0.05% through year 10

BMI, Body mass index; *HDL,* high-density lipoprotein.

Data from Hoerger TJ, Zhang P, Segel JE, et al. Cost-effectiveness of metabolic surgery for severely obese adults with diabetes. *Diabetes Care.* 33:1933-1939, 2010.

Physical activity and weight loss lower the risk of developing T2DM by 58% in high-risk individuals (American College of Sports Medicine and ADA, 2010). Physical activity decreases peripheral insulin resistance by improving glucose uptake by skeletal muscle cells. During muscle activity, glucose is transported into myocytes and used to replenish muscle glycogen stores. Glycogen is metabolized during exercise in a process known as glycogenolysis. Moderate exercise consisting of the use of 350 kcal of energy will result in improvement of peripheral insulin sensitivity over the course of 24 hours (Newsom et al., 2013). In T2DM, GLUT4 is impaired at rest but enhanced by the muscle contractions that occur during physical activity. Thus, insulin resistance at the periphery improves with exercise (Wang Y et al., 2009) Recommendations for T2DM physical activity prescribing are shown in Table 34-11.

Self-monitoring of blood glucose allows patients to evaluate their individual responses to lifestyle and pharmacologic interventions and to assess whether they are achieving their short-term glycemic targets. SBGM can also be used to detect extreme changes in blood glucose levels, including hypoglycemia, hyperglycemia, and DKA. Patients who successfully use SBGM can learn to adjust insulin doses, alter activity levels, and better understand the correlation between food intake and pharmacologic therapy.

Structured glucose testing is useful for recognizing specific problematic glycemic patterns such as hypoglycemia, fasting hyperglycemia, and postprandial hyperglycemia. Identifying the most likely cause of these patterns can assist patients in altering behaviors or changing medications or dosages to improve overall glycemic control (Polonsky et al., 2009). Structured testing can be performed before and after meals to determine the effect of food intake on glycemic excursions. Patients who perform SMBG before and after exercise will learn how insulin resistance at peripheral muscle sites appears to improve with mild to moderate activity performed 5 days per week. In addition, by testing pre- and postprandial blood glucose at breakfast for 2 or 3 days before initiating exercise, they can better determine at what time of day exercise will have the greatest glucose-lowering effect. When a patient beings an exercise program, this paired testing pattern is simply repeated, and exercise-related reductions in blood glucose can be identified. The same SMBG testing pattern can be repeated for each meal but should be individualized based on patients' eating, working, exercise, and sleeping habits.

The difference between premeal and 2-hour postprandial blood glucose levels is known as the Δ (or delta, a math symbol indicating the difference between two values). A physiological response to a meal should result in a positive Δ value of 0 to 50 mg/dL. For example, an insulin-requiring patient with T2DM checks his blood glucose before lunch and notes the blood glucose level as 100 mg/dL. He anticipates that he will require 8 units of rapid-acting insulin to cover the carbohydrates consumed for that meal. Two hours after eating, his postmeal glucose is 134, and his Δ is +34. This means that he administered the correct amount of insulin for that meal. The interpretation of Δ values resulting from structured SMBG around meals is explained in more detail in Table 34-12. Note that any negative Δ values 2 hours postprandially would indicate that the patient is at risk for developing postabsorptive hypoglycemia. Thus, patients with negative Δ values should continue monitoring their blood glucose 3 and 4 hours after the meal to ensure that they do not experience a rapid decline in blood glucose.

In summary, lifestyle intervention provides the foundation of care for all patients with diabetes. Patients at high risk for developing diabetes should be encouraged to increase their physical activity and to adopt a healthier meal plan in an attempt to reduce both their weight and their cardiometabolic risk. ILI appears to have a greater effect on inducing diabetes remission if it is initiated soon after patients

Table 34-11 Summary of Physical Activity Recommendations for Patients with Type 2 Diabetes Mellitus

- Perform at least 150 minutes of moderately intense physical activity (50%-70% of maximum heart rate) over at least 3 days/wk with no more than 2 consecutive days void of exercise.
- Indications for exercise stress testing:
  - Age >40 years with or without cardiovascular risk factors in addition to diabetes
  - Age >30 years plus:
    - T1DM or T2DM of a disease duration >10 years
    - Hypertension
    - Current cigarette smoker
    - Dyslipidemia
    - Proliferative or preproliferative retinopathy
    - Chronic kidney disease, including microalbuminuria
  - Known history of stroke, coronary artery disease, or peripheral vascular disease
  - Autonomic neuropathy
  - End-stage renal disease
- Unless contraindicated, patients should be encouraged to participate in resistance training (2 to 4 sets of 8 to 10 repetitions each) twice weekly.
  - Adults should train each major muscle group 2 or 3 days/wk using a variety of exercises and equipment.
  - Very light or light intensity is best for older people or previously sedentary adults starting exercise.
  - Two to four sets of each exercise will help adults improve strength and power.
  - For each exercise, 8 to 12 repetitions will improve strength and power, 10 to 15 repetitions will improve strength in middle-aged and older people starting exercise, and 15 to 20 repetitions will improve muscular endurance.
  - Adults should wait at least 48 hours between resistance training sessions.
  - Contraindications for resistance training include poor left ventricular function, unstable angina, proliferative diabetic retinopathy, cardiac autonomic neuropathy, a history of exercise-induced ventricular dysthymias, vertigo, and vestibular dysfunction.
- Monitor blood glucose before and after exercise. Proactively treat for hypoglycemia:
  - If pre-exercise blood glucose level is <100 mg/dL, patients using secretagogues or insulin should consume 15 g of carbohydrates before initiating physical activity.
  - Consuming 5 to 30 g of carbohydrates may be necessary to minimize hypoglycemia risk during intense or prolonged physical activity lasting more than 30 minutes.
- Patients requiring supervised cardiovascular rehabilitation programs include:
  - Those with cardiac autonomic neuropathy, coronary artery disease, peripheral vascular disease, stroke, proliferative retinopathy, macular edema, autonomic neuropathy (loss of sweating capacity), or peripheral neuropathy (increased risk of falls and foot ulcerations)

T1DM, Type 1 diabetes mellitus; *T2DM,* type 2 diabetes mellitus.
American College of Sports Medicine and American Diabetes Association, 2010; Bjarnason-Wehrens et al., 2004; Garber CE et al, 2011.

Table 34-12 Interpretation of Structured Self-Monitoring of Blood Glucose Δ Values*

Δ (mg/dL)	Interpretation	Intervention
0-50	Correct insulin was given for amount of carbohydrates consumed Correct lag time procedure was followed	None
51-100	Insulin-to-carbohydrate undercalculation Incorrect lag time Possible snacking between end of meal and 2-hour test	Increase prandial insulin dose by 1 to 2 units next time this type of food is eaten Make sure to inject insulin at least 15 minutes before meals
100-200	Patient possibly had elevated blood glucose before the meal and did not take a correction dose of insulin Insulin-to-carbohydrate mismatch Insulin may have been omitted Possible error in SMBG technique	Teach patient how to use a premeal insulin sensitivity factor (see discussion of physiological insulin replacement) If a patient omitted insulin, the Δ value illustrates the effect of this decision If postmeal Δ is consistently elevated, increase prescribed baseline insulin dose by 1 unit/day until Δ is 0-50 or 2-hour postprandial glucose is <140 mg/dL Educate patient on proper SMBG technique; touching fruit, cake, or ice cream after a meal may leave sugar deposits on the fingertips and result in falsely high SMBG results
Any negative value (e.g., −25)	Miscalculation of insulin-to-carbohydrate ratio; too much insulin bolused for amount of carbohydrates eaten; patient is likely to become hypoglycemic in the next 1 to 2 hours	Educate patient regarding insulin absorption principles: 1 hour after administering bolus, 90% of rapid-acting insulin analog remains in depot; 2 hours after bolusing, 60% of insulin remains in depot. Thus, if 10 units of insulin are given at 8:00 AM, 6 units remain to be absorbed at 10:00 AM. A premeal glucose value of 120 mg/dL and a 2-hour postprandial value of 90 mg/dL yield a Δ of −30 mg/dL. The patient still has 6 units remaining to be absorbed and is likely to become hypoglycemic. Appropriate surveillance and intervention should be initiated.

*The Δ value is calculated by determining the difference between the premeal and 2-hour postprandial glucose values. A physiological rise in 2-hour postprandial glucose levels from baseline in euglycemic individuals is ≤50 mg/dL.
SMBG, Self-monitoring of blood glucose.
Adapted with permission from Unger J. *Diabetes management in primary care.* 2nd ed. Philadelphia: Lippincott, Williams and Wilkins; 2012.

are diagnosed with impaired glycemic control. Patients should be referred to a registered dietitian soon after being diagnosed to receive their customized MNT and meal program.

The ADA and the American College of Sports Medicine encourage the prescribing of cardiovascular and resistance training for nearly all patients with diabetes. Before initiating any form of intensive physical activity, patients with a disease duration of longer than 10 years should undergo a stress test. Patients with advanced disease should exercise in a supervised environment.

Obese or overweight patients with T2DM may be considered candidates for antiobesity pharmacotherapeutic interventions, especially if they are at high risk for CVD. Patients who are unable to modify their weight should be referred to a bariatric surgeon.

The use of structured SMBG will allow patients to determine patterns of glycemic control in relation to the use of their medications, meals, and exercise habits. In addition, structured SMBG may be useful in predicting the onset of hypoglycemia.

MEDICAL MANAGEMENT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

The goals of therapeutic intervention in patients with T2DM are to (1) encourage the adoption of healthy lifestyle choices (i.e., cease alcohol, nicotine, and substance abuse; follow a healthful eating plan; and increase physical activity); (2) encourage modest weight reduction (5%-10% from baseline); and 3) introduce safe, effective, and rational pharmacologic interventions in a timely manner that will allow patients to achieve their customized metabolic targets. Primary care physicians are actively involved in screening, diagnosing, and managing patients with diabetes; 90% of all patients with diabetes are managed in the primary care setting. Diabetes is a multifactorial disease state that is chronic and progressive. As such, its management requires frequent reassessment and adjustment.

ENCOURAGING PATIENT SELF-CARE

Clinicians should be viewed as "coaches" who direct diabetes care, although patients are ultimately responsible for carrying out the complex daily self-management regimen. Unlike with other chronic diseases such as cancer, patients with diabetes are required to make multiple decisions each day that may affect their glycemic control. Glucose levels may vary based on physical activity, sleep duration, timing and dosing of antihyperglycemic therapies, food consumption, macronutrient intake, renal and hepatic status, concomitant prescribed medications, recent history of hypoglycemia, and accuracy of SMBG technique. Therefore, patients must take an active role to achieve their metabolic targets and successfully manage their diabetes.

Diabetes self-management can become all-encompassing and distressful. Patients with diabetes have to make choices and decisions throughout each day in hopes of keeping their blood glucose levels within the physiological range of 90 to 130 mg/dL. Patients should never be blamed for failing to achieve their fasting blood glucose, postprandial glucose, or A1C targets. Instead, clinicians must work with patients to provide the tools they need to become successful at diabetes self-management.

When euglycemic individuals eat, their glucose levels are maintained within a narrow range (85-126 mg/dL). This

occurs because the normally functioning pancreas is provided with neuroendocrine signals, allowing its α and β cells to coordinate the perfect level of insulin secretion to cover the carbohydrates consumed in each meal. Patients with diabetes have multiple physiological deficits. Over time, their β-cell function deteriorates to the point at which insulin must be used to maintain adequate control of plasma glucose levels. When insulinopenic patients eat, exogenous insulin must be given based on a dose calculation they determine before each meal. Dose determinations are not always simple, and by no means are they always correct. Patients have to substitute their brain for their pancreas to control their glycemia and self-manage their disease. Therefore, criticism of patients with diabetes should be tempered at all times, and patients should be encouraged to attain the best level of glycemic control of which they capable.

INDIVIDUALIZED METABOLIC TARGETS

Randomized controlled trials such as the DCCT in patients with T1DM (DCCT Research Group, 1993) and the UKPDS (U.K. Prospective Diabetes Study Group, 1998) and Kumamoto Study (Ohkubo et al., 1995) in those with T2DM established glycemic therapeutic goals that minimize the risk of long-term complications. Neither the DCCT nor the UKPDS was successful at maintaining A1C levels below 7% in their intensively treated cohorts.

More recently, published RCTs have attempted to intensify patients' glycemic control to a target A1C below 6.5% using a variety of interventions. The primary objective of the ACCORD study (ACCORD Study Group, 2008) was to decrease CVD in high-risk patients. More than 10,000 patients either with or at risk for developing CVD were randomized either to an intensive intervention targeting an A1C level of less than 6.0% or to an intervention with a more conservative A1C target of less than 7.9%. The intensively treated cohort demonstrated a 22% higher rate of cardiovascular mortality than the more conservatively managed patients. Based on ACCORD data, the ADA now recommends that clinicians consider patients' disease duration, severity of comorbidities, hypoglycemia history, and life expectancy when setting individualized metabolic targets. Patients deemed to be at high risk should have an A1C target of 7.5% to 8%, but most healthy patients should be treated to an A1C target of 6.5% or less to 7% (ADA, 2013b; Ismail-Beigi et al., 2011).

Some have speculated that the excess mortality rate in ACCORD may have been related to hypoglycemia. Interestingly, however, severe hypoglycemia was associated with an increased risk of death in the more conservative treatment cohort more so than in the intensively managed cohort (Bonds et al., 2012). Additionally, severe hypoglycemia events were more prevalent in patients having a higher baseline A1C; those with A1C levels closer to the 7% target had more frequent, but less severe, hypoglycemia episodes. Hypoglycemia results in the release of counterregulatory hormones, including cortisol, norepinephrine, and epinephrine. Hypoglycemia may also increase the risk of QTc prolongation (Beom et al., 2013). Patients who experience QTc prolongation during an episode of severe hypoglycemia would be subject to potentially fatal arrhythmias (i.e., torsades de pointes ventricular tachycardia) induced by the release of catecholamines (Figure 34-1).

Could repeated episodes of hypoglycemia be protective against sudden death, as observed in ACCORD patients who were closer to the prescribed A1C target? A single episode of hypoglycemia will result in defective counterregulation and a blunted adrenergic response to future events. Additionally, patients who become hypoglycemic lose their ability to recognize the symptoms of low blood glucose. Thus, hypoglycemia awareness autonomic failure (also called "hypoglycemia unawareness") may result in a form of hypoglycemia preconditioning that protects against the development of a fatal arrhythmia.

Patients with suboptimal glycemic control who are ambitiously treated to a fasting glucose or A1C level based on politically motivated incentive payment programs may be at risk for developing fatal arrhythmias. Clinicians must consider all aspects of patients' medical, behavioral, and social history before determining their optimal individualized glycemic targets.

Metrics other than A1C are also important to evaluate to identify and mitigate each patient's long-term risk for complications. Hirsch and Brownlee have suggested that A1C and duration of diabetes (glycemic exposure) accounted for only 11% of the total risk in the retinopathy cohort of T1DM patients in the DCCT (Hirsch and Brownlee, 2010). The remaining 89% of a patient's likelihood for developing microvascular complications may be derived from genetics, environmental factors, poorly controlled lipids, and hypertension. Although targeting glycemic control patients is a noble goal, clinicians must never forget the complex metabolic nature of T2DM. Normalization of lipids, blood pressure, and renal function cannot be overshadowed by the struggle to become a "glycemic perfectionist."

The ADA and AACE have each published statements providing a framework for initiating and titrating pharmacologic therapies for patients with T2DM in the primary care setting (ADA, 2013b; Garber et al., 2013) A summary of the highlights for the AACE comprehensive diabetes management algorithm is offered in Table 34-13. Both the ADA and AACE statements include recommended metabolic treatment targets, which are summarized in Table 34-14. Clinicians should remember that managing patients with diabetes entails customizing targets for blood pressure, weight, and lipids, in addition to glycemia.

The American Academy of Family Physicians has yet to publish any guidelines on diabetes management. Patients are unique entities with individual concerns, fears, and abilities to address their given disease state. Primary care physicians must never lose sight of the importance of directing individualized care toward what is safe and efficacious for each patient.

PHARMACOLOGIC MANAGEMENT OF TYPE 2 DIABETES MELLITUS

After pharmacotherapy is initiated, patients must become even more active participants in their diabetes self-management. Performing SMBG, adhering to MNT and physical activity recommendations, and undergoing professional surveillance to determine whether metabolic targets

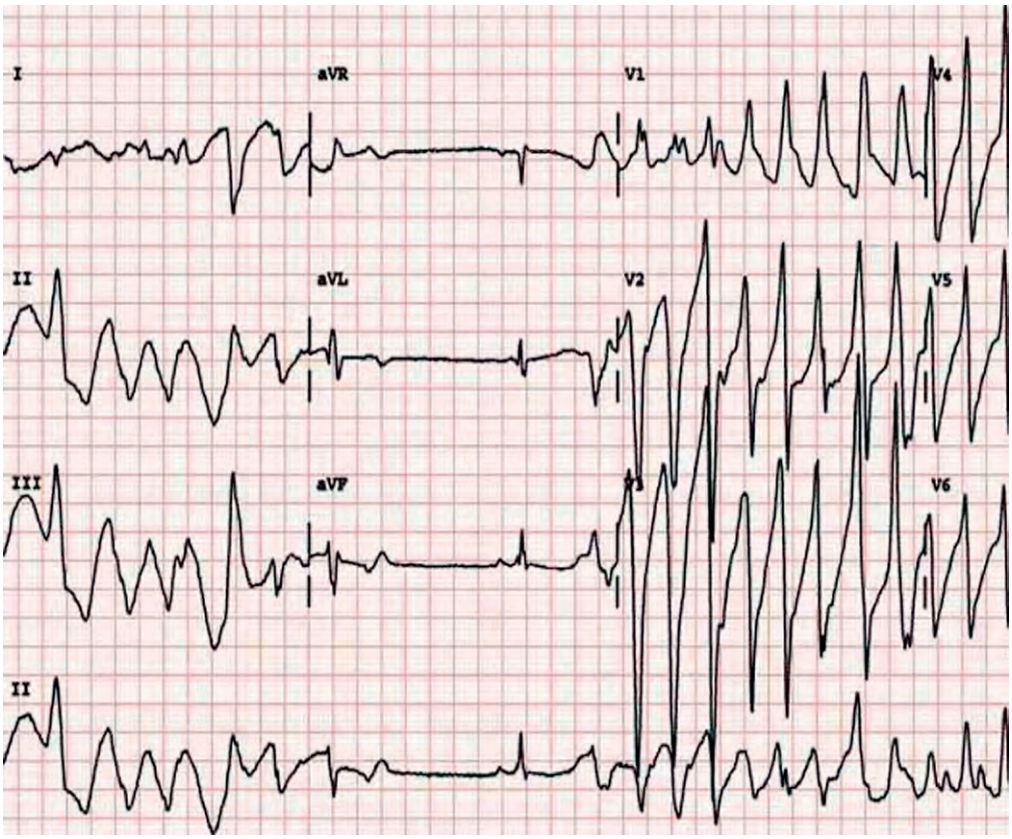

Figure 34-1 Torsades de pointes is a distinctive form of polymorphic ventricular tachycardia characterized by a gradual change in the amplitude and twisting of the QRS complexes around the isoelectric line. Torsades de pointes is associated with a prolonged QTc interval, which may be congenital or acquired. The arrhythmia usually terminates spontaneously but may reoccur and degenerate into a fatal form of ventricular fibrillation.

Table 34-13 Summary of the American Association of Clinical Endocrinologists 2013 Treatment Algorithm for Diabetes

- Lifestyle intervention remains the foundation of diabetes care across all A1C levels.
- If a patient's A1C is ≥9%, initiate and titrate basal insulin.
- Patients with an A1C <7.5% may be treated with monotherapy, as follows:
  - Metformin is considered first-line therapy.
  - Second-line therapies include GLP-1 receptor agonists, DPP-4 inhibitors, and α-glucosidase inhibitors.
  - If A1C is >6.5% after 3 months of therapy, add a second agent.
- Consider dual or triple combination therapy in patients with A1C levels ≥7.5% and ≤9%, as follows:
  - GLP-1 receptor agonists and DPP-4 inhibitors are the preferred agents.
  - Basal insulin may also be used.
  - SGLT2 inhibitors are acceptable drugs for combination therapy (ADA guidelines do not mention SGLT2 inhibitors).
  - If A1C is not at goal after 3 months, add a third agent.
- For patients who are symptomatic with an A1C of 8.5%, initiate basal insulin.
- Practical strategies to consider when customizing pharmacologic intervention include:
  - Prescribe medications that are less likely to result in hypoglycemia.
  - Medications that minimize weight gain should be preferred.
  - A1C testing should be repeated every 3 months until patients achieve their individualized goals.
  - Lifestyle intervention should be emphasized at each visit.
  - Smoking is unacceptable; encourage patients to stop nicotine use. Patients may be referred to 800-QUIT-NOW for free smoking cessation assistance.
  - Combination therapy using agents with complementary mechanisms of action is often required to help patients to achieve their prescribed glycemic targets.
  - When using insulin, DPP-4 inhibitors, SGLT2 inhibitors, metformin, GLP-1 receptor agonists, and bromocriptine may be continued. Sulfonylureas and thiazolidinediones should be discontinued because of increased risks of weight gain and hypoglycemia.
- Cost is important, but safety trumps cost.

ADA, American Diabetes Association; *DPP-4,* Dipeptidyl peptidase-4; *GLP-1,* glucagon-like peptide 1; *SGLT2,* sodium–glucose co-transporter 2.
Adapted from Garber AJ, Abrahamson MJ, Barzilay JI, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement: executive summary. *Endocr Pract.* 19:536-557, 2013.

Table 34-14 Metabolic Treatment Targets for Most Patients with Diabetes

Metabolic Target	AACE Guidelines	ADA Guidelines
A1C (%)	≤6.5	≤7.0
Fasting or premeal blood glucose (mg/dL)	<110	70-130
2-hour postprandial blood glucose (mg/dL)	<140	<180
Blood pressure (mm Hg)	<130/80	<140/80
LDL cholesterol (mg/dL)	<100 (<70 for high-risk patients with CVD)	<100
HDL cholesterol (mg/dL)	>40 for men; >50 for women	>50
Triglycerides (mg/dL)	<150	<150

AACE, American Association of Clinical Endocrinologists; *ADA,* American Diabetes Association; *CVD,* cardiovascular disease; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein.

Adapted from Garber AJ, Abrahamson MJ, Barzilay JI, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement: executive summary. *Endocr Pract*. 19:536-557, 2013; American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care*. 36(suppl 1):S11-S66, 2013.

are being achieved are all necessary to lessen the impact of diabetes-related complications.

Patients should be aware of the potential risks and clinical benefits of the different types of oral agents. Some medications may increase weight or induce hypoglycemia; others must be held before undergoing certain diagnostic procedures. The continued use of oral agents during acute inpatient care may be detrimental. Insulin is the preferred drug for patients with diabetes who are admitted to the hospital for acute illness. Insulin also may be necessary in certain situations that complicate T2DM management, including concomitant use of corticosteroids, surgery, restricted oral nutrient intake, and pregnancy. Table 34-15 lists the noninsulin medications currently approved for patients with T2DM, as well as their mechanisms of action and safety concerns. Information on dosing adjustments required for incretin agents based on renal status is provided in Table 34-16.

In summary, clinicians should individualize metabolic targets for patients with diabetes. Lifestyle intervention remains the foundation of care for all patients with diabetes. Patients whose glycemic control deteriorates over time should be ambitiously managed initially with metformin or a combination of medications designed to address their particular pathophysiological defects. Treatment-naive patients will likely have some remaining β-cell function at the time of diagnosis and should respond to oral agents or incretins. Over time, β-cell function and mass will deteriorate, necessitating the use of insulin to control fasting and postprandial glucose excursions. Pharmacotherapy agents that have a low risk for potentiating hypoglycemia and weight gain should be preferred. Specific agents should be selected based on their likely effectiveness in reducing blood glucose levels to patients' individualized target range while taking into consideration patients' unique characteristics and preferences.

INSULIN INITIATION FOR PATIENTS WITH TYPE 2 DIABETES MELLITUS

Insulin is the most powerful tool in the diabetes pharmacologic armamentarium. Timely initiation of exogenous insulin appears to reduce insulin resistance and induce β-cell rest and does not increase cardiovascular or cancer risk over time (Gerstein et al., 2012). Thus, insulin initiation should be considered for symptomatic patients who have an A1C higher than 8.5% or for any patients who have an A1C higher than 9.0%. Basal insulin is simple to initiate and may be used safely in combination with several oral agents and with GLP-1 receptor agonists.

Type 2 diabetes mellitus is a progressive disease. Therefore, its effective treatment requires early initiation of appropriate therapies, frequent monitoring, and reassessment to make certain that therapeutic goals are attained.

Exposure to chronic hyperglycemia can cause micro- and macrovascular complications, many of which may already be apparent at the time of diabetes diagnosis. Multiple defective metabolic pathways work to overcome the body's defensive mechanisms, resulting in loss of β-cell function and mass. Ultimately, genetically prone individuals whose β cells become exposed to a progressively antagonistic metabolic environment will demonstrate apoptosis. As endogenous insulin levels are unable to prevent lipolysis, plasma FFA concentrations increase, further promoting apoptosis. FFAs also impair the body's first-phase insulin response and amplify hepatic glucose production. FFAs potentiate peripheral insulin resistance by blocking the ability of GLUT4 to transport glucose from the plasma into the myocytes. Patients exposed to chronic hyperglycemia may or may not experience symptoms similar to those with poorly controlled T1DM (i.e., fatigue, thirst, weight loss, hunger, frequent urination, and dry skin secondary to dehydration).

Intensified and individualized therapy targeting glycemic control is crucial for reducing the incidence of microvascular complications in patients with T2DM. Evidence supports efforts that appear to induce "metabolic memory," a theoretical protective mechanism through which early reversal and avoidance of hyperglycemia appear likely to minimize the risk of developing long-term complications (DCCT/EDIC Research Group, 2005). The fact that early initiation of intensive insulin therapy reduces insulin resistance and appears to induce β-cell rest suggests that such a regimen should be initiated sooner rather than later in treatment-naive patients with T2DM (Weng et al., 2008).

Recent RCTs have demonstrated that insulin interventions can be readily initiated and successfully titrated in the primary care setting (Gerstein et al., 2006; Meneghini et al., 2007) Additionally, with few exceptions, "needle phobia" often is less of an issue for patients than for clinicians. Most patients are willing to intensify their diabetes management according to the best guidance provided by their physicians. Clinicians are encouraged to develop several basal and prandial insulin protocols (perhaps using insulin pens or even disposable insulin patch pump devices) that can be introduced easily to patients (Figure 34-2).

Before initiating an insulin regimen, clinicians must consider patients' eating, sleeping, and exercise patterns and their ability to carry out diabetes self-management tasks. Perhaps most important, patients will need education

Table 34-15 Food and Drug Administration–Approved Noninsulin Pharmacologic Agents for Type 2 Diabetes Mellitus Treatment

Agents (Trade Name[s])	Mode of Action	Safety Concerns, Within-Class Distinctions, and Other Important Considerations
SULFONYLUREAS		
Glyburide (Micronase, Diabeta) Glipizide (Glucotrol) Glipizide-GITS (Glucotrol XL) Glyburide, micronized (Glynase) Glimepiride (Amaryl)	Insulin secretagogue	Increase the risk of hypoglycemia, especially in elderly adults and those with renal insufficiency or weight gain Meta-analysis suggests that sulfonylureas may increase stroke risk (Monami et al., 2013b) Short effective durability of drug except in patients with monogenetic T2DM (i.e., maturity-onset diabetes of the young) Glimepiride lowers fasting and postprandial glucose and has the best safety profile; avoid glyburide in elderly patients and those with CVD
BIGUANIDES		
Metformin (Glucophage) Metformin XL (Fortamet) Metformin XR (Glucophage XR, Glumetza) Metformin oral suspension	Decrease hepatic glucose production and glucose absorption from the GI tract and increase peripheral utilization of glucose	Must take with food to avoid gastritis and GI side effects Caution required for use in elderly patients and those with an estimated GFR rate <45 mL/min Withhold before contrast studies are performed; metformin may be restarted after serum creatinine is repeated and determined to be within a safe targeted range ≤10% of patients may be intolerant to side effect profile May reduce cancer risk in some patients with diabetes May improve fertility in patients with PCOS Some diabetologists prefer a dosing protocol involving rapid titration from 500 mg/day extended release with food to 2 g/day over 2 weeks
α-GLUCOSIDASE INHIBITORS		
Acarbose (Precose) Miglitol (Glyset)	Slow gut absorption of carbohydrates by inhibiting α-glucosidase enzymes	Contraindicated in inflammatory bowel disease, malabsorption syndromes, and partial bowel obstructions May induce hypoglycemia when used in combination therapy; oral glucose (dextrose), whose absorption is not inhibited by α-glucosidase inhibitors, should be used instead of sucrose (cane sugar) for hypoglycemia treatment; hypoglycemia will also respond to glucagon injection Glycemic efficacy of acarbose has been noted to be equal to that of metformin in treatment naive Chinese patients (Yang et al., 2014)
THIAZOLIDINEDIONE		
Pioglitazone (Actos)	Enhances tissue sensitivity to insulin in skeletal muscles by activating intracellular peroxisome proliferator-activated receptors	May cause resumption of ovulation in anovulatory premenopausal women Cases average weight gain of 0.9-2.6 kg Contraindicated in any patient with advanced heart failure (NYHA class III or class IV) or a history of bladder cancer Liver function testing required at baseline and every 2 months for the first year and then periodically thereafter Increases fracture risk in women
GLITINIDES		
Repaglinide (Prandin) Nateglinide (Starlix)	Rapid-acting insulin secretagogue with short (1- to 2-hour) duration of action; same mechanism of action as sulfonylureas but with a different binding site to pancreatic β cells	More effective than metformin, sulfonylureas, and thiazolidinediones at lowering postprandial blood glucose Less risk of hypoglycemia than sulfonylureas because of more rapid kinetics Must be taken 15 minutes before meals Approximately 1 month of therapy is required before fasting blood glucose decreases May either be weight neutral or result in slight weight increase
D2-DOPAMINE AGONIST		
Bromocriptine (Cycoset)	Resets dopaminergic and sympathetic tone within the central nervous system	Reduces glucose, triglycerides, and insulin resistance in patients with T2DM Can be used with all other oral agents and insulin Should be taken daily within 2 hours of rising Consider for use in patients who are shift workers; improving dopaminergic and sympathetic tone within the SCN may reduce insulin resistance; shift workers have disruption in their SCN pacemaker
BILE ACID SEQUESTRANT		
Colesevelam (Welchol)	Uncertain mode of action; may affect secretion of GLP-1	Not indicated as monotherapy in T2DM; may be used with metformin or metformin + sulfonylurea May be considered for off-label use in patients with prediabetes to reduce LDL cholesterol to <100 mg/dL and preserve β-cell function May be considered for use in T2DM patients who have elevated LDL cholesterol

Continued on following page

Table 34-15 Food and Drug Administration–Approved Noninsulin Pharmacologic Agents for Type 2 Diabetes Mellitus Treatment (Continued)

Agents (Trade Name[s])	Mode of Action	Safety Concerns, Within-Class Distinctions, and Other Important Considerations
DPP-4 INHIBITORS		
Sitagliptin (Januvia) Sitagliptin + metformin/sitagliptin + metformin, extended release (Janumet/Janumet XR) Saxagliptin (Onglyza) Saxagliptin + metformin, extended release (Kombiglyze XR) Linagliptin (Tradjenta) Linagliptin + metformin (Jentadueto) Alogliptin (Nesina) Alogliptin + metformin (Kazano) Alogliptin + pioglitazone (Oseni)	Block the action of DPP-4 enzymes, resulting in a two- to threefold increase in plasma levels of endogenous GLP-1	Most common side effects are rash and rhinitis Doses of all DPP-4 inhibitors, with the exception of linagliptin, must be adjusted based on renal status (see Table 34-15) As a class, DPP-4 inhibitors do not appear to increase the risk of CAD, HF, or hospitalizations for CHF; they also do not mitigate cardiovascular risk (Monami et al., 2013a) Oseni is contraindicated in patients with established NYHA class III or class IV HF and is not recommended in patients with symptomatic HF
GLP-1 RECEPTOR AGONISTS		
Exenatide (Byetta) Liraglutide (Victoza) Exenatide QW (Bydureon)	Enhance nutrient-stimulated insulin secretion via activation of GLP-1 receptors on β cells; inhibit glucagon secretion; delay gastric emptying; reduce appetite	Associated with weight loss Favorable effect on cardiovascular biomarkers Low rates of hypoglycemia Favor preservation of β-cell function GLP-1 infusion studies demonstrate favorable effects on endothelial cell function in humans Direct link to acute pancreatitis has not been demonstrated Contraindicated in patients with personal or family history of medullary thyroid carcinoma or MEN II (medullary thyroid cancer + pheochromocytoma) Most common adverse effect is nausea, which can be avoided if patients do not eat beyond the point of satiety When used with insulin secretagogue or insulin, reduce dose of secretagogue or insulin to minimize the likelihood of inducing hypoglycemia Exenatide is injected twice daily within 1 hr of eating; liraglutide is injected once daily without regard to meals; exenatide QW is injected once weekly Contraindicated in patients with a history of pancreatitis. Pancreatitis has been observed in patients taking GLP-1 receptor agonists or DPP-4 inhibitors. However, no direct signal has been noted that would implicate the incretin class as inducers of pancreatitis or pancreatic cancer in patients with diabetes Discontinue use in patients suspected of having pancreatitis Exenatide QW may cause injection nodules
SYNTHETIC AMYLIN ANALOG		
Pramlintide (Symlin)	Exogenous replacement of amylin, which is deficit in proportion with insulin deficiency in diabetes	Adjunct treatment in patients with T1DM or T2DM who use mealtime insulin therapy and have not achieved desired glucose control despite optimal insulin therapy May be used with or without sulfonylurea or metformin in T2DM Injected before meals Adverse effects include nausea and severe hypoglycemia Should be used only in patients who do not have hypoglycemia awareness autonomic failure (i.e., hypoglycemia unawareness) Can result in weight loss and satiety Challenging to titrate
SGLT2 INHIBITOR		
Canagliflozin (Invokana)	Reduces the renal threshold of glucose absorption from 180 g/day to approximately 70 g/day by blocking the SGLT2 co-transporter in the distal tubules of the glomeruli. Because glucose is not absorbed in the plasma, insulin resistance improves in a glucose-dependent manner, and patients experience a reduction in fasting and postprandial glucose levels, A1C, weight, and BP.	Side effects include increased frequency of urination, glycosuria, UTIs, mycotic infections, and diarrhea. Elderly patients should be carefully observed for treatment-induced orthostatic hypotension. Contraindicated in patients with renal insufficiency and a GFR <45 mL/min/1.73 m^2 Canagliflozin dose should be 100 mg/day taken in the morning if the estimated GFR is 45-60 mL/min/1.73 m^2; can be titrated to 300 mg if the GFR is >60 mL/min/1.73 m^2 Co-administration with nonselective inducers of UGT enzymes (Rifampin, phenytoin, phenobarbital, ritonavir) will decrease the efficacy of canagliflozin

Table 34-15 Food and Drug Administration–Approved Noninsulin Pharmacologic Agents for Type 2 Diabetes Mellitus Treatment (Continued)

Agents (Trade Name[s])	Mode of Action	Safety Concerns, Within-Class Distinctions, and Other Important Considerations
Dapagliflozin (Farxiga)	Starting dose is 5 mg daily. Can increase to 10 mg daily for patients requiring additional glycemic control	Should not be initiated in patients with an eGFR <60 mL/min/1.73 m^2
	As with other agents in this class, SGLT2 inhibitors interfere with 1,5-anhydroglucitol assays	Results in approximately 70 g of glucose excretion in urine weekly
Empagliflozin (Jardiance)	Doses are 10 and 25 mg daily	Do not initiate in patients with eGFR <45 mL/min/1.73 m^2 and discontinue if eGFR is persistently <45 mL/min/1.73 m^2

BP, Blood pressure; *CAD,* coronary artery disease; *CHF,* congestive heart failure; CVD, cardiovascular disease; *DPP-4,* Dipeptidyl peptidase-4; *GFR,* glomerular filtration rate; *GI,* gastrointestinal; *GLP,* glucagon-like peptide; *HF,* heart failure; *LDL,* low-density lipoprotein; *MEN,* multiple endocrine neoplasia; *NYHA,* New York Heart Association; *PCOS,* polycystic ovary syndrome; *SCN,* syprachiasmic nucleus; *T2DM,* type 2 diabetes mellitus; *UTI,* urinary tract infection.

Boehringer Ingelheim Pharmaceuticals and Eli Lilly: Jardiance product information. http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Jardiance/jardiance.pdf. Assessed November 2014; Bristol-Myers Squibb and AstraZeneca Pharmaceuticals: Farxiga product information. http://www.azpicentral.com/farxiga/pi_farxiga.pdf. Accessed November 2014; Janssen Pharmaceuticals: Invokana product information. http://www.invokanahcp.com/prescribing-information.pdf. Accessed November 2014; Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab.* 15:938-953, 2013; Yang W, Liu J, Shan Z, et al. Acarbose compared with metformin as initial therapy in patients with newly diagnosed type 2 diabetes: an open-label, non-inferiority randomised trial. *Lancet Diabetes Endocrinol.* 2013; doi: 10.1016/S2213-8587(13)70021-4; Monami M, Ahren B, Dicembrini I, et al. Dipeptidyl peptidase-4 inhibitors and cardiovascular risk: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab.* 15:112-120, 2013.

Table 34-16 Dosing Adjustments Required for Incretin Agents Based on Renal Status

Drug	Mild Renal Insufficiency*	Severe Renal Insufficiency or Disease Requiring Dialysis†
DPP-4 INHIBITORS		
Linagliptin	No adjustment required	No adjustment required
Saxagliptin	No adjustment required	Reduce to 2.5 mg/day
Sitagliptin	50 mg/day	25 mg/day
Alogliptin	≥30 to ≤60 mL/min use 12.5 mg/day	6.25 mg/day
GLP-1 RECEPTOR AGONISTS		
Exenatide	Use with caution	Contraindicated
Exenatide QW	Use with caution	Contraindicated
Liraglutide	Use with caution	Use with caution

*Creatinine clearance ≥50 mL/min; serum creatinine ≤1.7 mg/dL in men and <1.5 mg/dL in women.

†Creatinine clearance <30 mL/min; serum creatinine >3.0 in men and >2.5 in women.

DPP-4, Dipeptidyl peptidase-4; *GLP-1,* glucagon-like peptide 1.

References: Amylin Pharmaceuticals, 2013; Boehringer Ingelheim, 2011; Bristol-Myers Squibb, 2011, 2013; Monami et al., 2014; Merck, 2011; Novo Nordisk, 2013; Takeda, 2013.

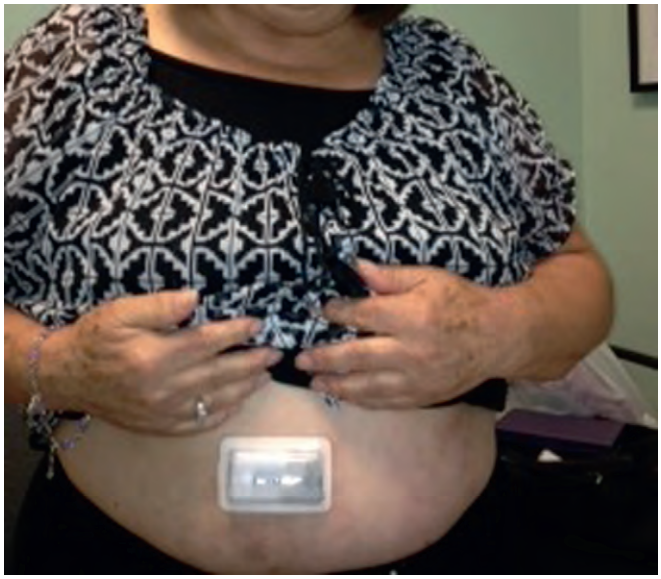

Figure 34-2 Patient displaying a V-Go disposable insulin patch pump (Valeritas, Bridgewater, NJ). Designed for use in patients with type 2 diabetes mellitus and available in three sizes (V-Go 20, V-Go 30, and V-Go 40), these devices deliver rapid-acting lispro or aspart insulin at a single specific basal rate of 0.83, 1.25, or 1.67 units/hr. An additional 36 units of prandial (bolus) insulin may be delivered by the patient before meals or for correction dose if glucose levels are elevated. Patients must remove and replace the pump after 24 hours. The advantages of the pump include improvement in A1C, adherence to mealtime bolus insulin prescribing, no visual association with needle therapy, and a reduction in total daily Insulin dose (Rosenfeld and Grunberger, 2013). Most patients can learn to use the V-Go system in 5 to 10 minutes.

about how to prevent, predict, and effectively manage hypoglycemia.

Optimal insulin replacement regimens replicate physiological insulin secretion in the fasting and postabsorptive states. Euglycemic individuals produce sufficient insulin to maintain plasma glucose levels in the range of 85 to 140 mg/dL. Exogenous basal insulin replacement is prescribed to reduce the magnitude of excessive hepatic glucose production in the fasting state. The two available basal insulin analogs are glargine and detemir. Both are characterized by a relatively flat time-action profile with an onset of action within 1 to 4 hours. A double-blind, randomized, crossover, investigator-initiated study of once-daily dosing demonstrated that the pharmacokinetics (i.e., absorption, metabolism, distribution, and excretion) and pharmacodynamics (i.e., variability of absorption from injection site, time to peak effect, and duration of action) of these insulin analogs were equivalent (King, 2009).

Table 34-17 Simple Basal Insulin Protocols That May Be Effectively and Efficiently Initiated in the Primary Care Setting

Protocol	Initial Dose of Basal Insulin	Titration Schedule	Comments	Reference(s)
Canadian INSIGHT Trial	10 units at 9:00 PM	Increase dose by 1 unit at 9:00 PM daily until fasting glucose is ≤110 mg/dL.	Very simple titration schedule Can also increase dose by 5 units every Monday instead of adjusting daily	Gerstein et al., 2006.
PREDICTIVE 303 Protocol TITRATE Protocol	10 units at 9:00 PM	Perform SMBG every morning and base insulin dose on 3-day average of glucose values. The target fasting glucose is 80-110 mg/dL. Adjust 9:00 PM dose based on the average fasting glucose level over 3 days as follows: <80 mg/dL = –3 units 80-110 mg/dL = no adjustment >110 mg/dL = +3 units	Treatment goals can be modified. TITRATE study targets were set at 70-90 mg/dL. PREDICTIVE 303 Protocol should be considered perpetual; patients should not stop adjusting doses unless instructed by their clinicians.	Meneghini et al., 2007; Blonde et al., 2009
Insulin-Resistant Weight Protocol	0.4 units/kg of body weight at 9:00 PM	For patients who are obese, treatment-naive, and have symptomatic hyperglycemia who require a more rapid method of insulin initiation and titration; can increase the dose by 5 units each Monday up to a maximum of 60 units. After a patient has reached the 60-unit dose of basal insulin, add prandial insulin targeting a specific meal ("basal-plus" regimen) or reduce the basal dose by 20% and initiate either exenatide or liraglutide.	Can use in combination with a GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, or prandial insulin Continue metformin unless patient is metformin intolerant.	Unger, 2011

DPP-4, Dipeptidyl peptidase-4; *GLP-1,* glucagon-like peptide 1; *SMBG,* self-monitoring of blood glucose; *T2DM,* type 2 diabetes mellitus.

Approximately 60% of patients with T2DM are able to achieve an A1C of 7% or less using basal insulin replacement in combination with oral agents or a GLP-1 receptor agonist. Patients who are still unable to achieve their target fasting, postprandial, or A1C goals should be transitioned to a basal-plus (basal insulin plus one prandial injection at the largest meal) or basal-bolus (basal insulin plus prandial injections for all meals) insulin regimen that provides long-acting insulin for basal needs and rapid-acting insulin (i.e., lispro, aspart, or glulisine) to minimize the peak rise in glucose levels after carbohydrate ingestion.

Table 34-17 lists several practical regimens that may be used to initiate patients on basal insulin. Successful initiation of basal insulin requires patients to understand their individualized glycemic targets and to know how to safely achieve these objectives. In clinical trials, patients who are provided with a specific algorithm are almost always able to safely and effectively lower their A1C to their prescribed target. Thus, allowing patients to self-titrate should be the rule rather than the exception.

Table 34-18 lists the appropriate time to consider adding prandial insulin to one's basal regimen. Physiological insulin regimens should be individualized and titrated based on the factors shown in Table 34-19. Rapid-acting insulin analogs exhibit a peak onset of pharmacodynamics (blood glucose–lowering capacity) 60 minutes after injection. Peak carbohydrate absorption after a meal occurs 75 to 90 minutes after eating. Thus, to synchronize the peak activity of insulin with the expected risk in postprandial glucose, the analog should be injected 15 minutes before meals unless premeal blood glucose is less than 80 mg/dL (Unger, 2011). The delay between the time of injection and the start of the meal is known as the "lag time." Patients who inject just before eating may experience postprandial hypoglycemia within 1 hour of starting the meal only to develop postprandial hyperglycemia 2 to 3 hours later.

Table 34-18 Practical Considerations for Initiating Prandial Insulin

Consider adding prandial insulin:
- For patients who have not attained the recommended A1C of ≤7% despite successful basal insulin dose titration and the achievement of fasting glucose levels of <100 mg/dL (An alternative to starting prandial insulin is to add an incretin-based therapy to basal insulin, which will reduce postprandial and fasting glucose levels; however, exenatide QW is not approved for use with insulin.)
- When basal insulin dose titration has resulted in repeated episodes of nocturnal hypoglycemia
- When the basal insulin dose has exceeded 60 units/day
- For patients who have not met their A1C goal within 1 year of initiating basal insulin
- If the "BeAM factor" is >55 mg/dL
  - BeAM factor: the difference between bedtime and morning ("AM") blood glucose levels
  - Patients titrating basal insulin to a fasting glucose target of ≤100 mg/dL who have a BeAM factor >55 mg/dL are less likely to achieve an A1C ≤7% without experiencing nocturnal hypoglycemia; therefore, these patients should initiate prandial insulin
  - A BeAM factor >55 mg/dL is associated with an increased risk of nocturnal hypoglycemia, but not overall hypoglycemia

Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med*. 361:1736-1747, 2009; Zisman A, Aleksandra V, Zhou R. The BeAM factor: an easy-to-determine, objective, clinical indicator for when to add prandial insulin vs. continued basal insulin titration. Presented at the American Diabetes Association 71st Scientific Sessions (Abstract 1121-P), San Diego, CA, June 2011.

For a basal-plus regimen (basal insulin plus one prandial dose per day), identifying the meal to target for intervention might be simplified with the use of structured SMBG, as described in the Type 1 Diabetes Mellitus section of this chapter. SMBG should be performed before and 2 hours after each meal for 3 days. The meal with the highest Δ (difference between premeal and 2-hour postprandial

Table 34-19 Factors to Be Considered When Prescribing Physiological Insulin Replacement Therapy

Factor	Comment
Meal consumption	Does patient skip meals? Are meals consumed on a scheduled basis? What are the approximate sizes and carbohydrate contents of meals? Has patient received meal planning education from a registered dietitian or certified diabetes educator? Does patient have an eating disorder?
Work schedule	Does patient work irregular shifts? Does an irregular work schedule affect sleep? Does patient frequently travel? Does travel schedule require flexible meal and insulin injection scheduling?
Adherence history	Does patient have a history of omitting insulin doses? Is patient willing to perform frequent SMBG? Does patient understand how to properly perform SMBG and interpret glucose values, patterns, and averages?
Physical activity	Does patient exercise? What type of exercise does patient do? What time of day does exercise occur? Does exercise time vary? Is patient a professional athlete? Is patient planning to initiate an exercise program for the first time? What are patient's glucose targets before, during, and after exercise? Does patient know how to predict and treat hypoglycemia?
Hypoglycemia history	Does patient have a history of hypoglycemia unawareness? Does patient live alone? Does patient know how to predict and treat hypoglycemia? Are there comorbidities (e.g., heart disease, chronic kidney disease, seizures, hypoglycemia unawareness) that could preclude patient from being intensively managed and thereby increasing their risk of hypoglycemia? Does patient have access to and wear a CGM device? Does patient know to perform SMBG before driving? What is patient's target A1C?
Comorbidities of concern	Coronary artery disease or cardiac arrhythmias Preconception planning or pregnancy Cancer End-stage renal disease Mental illness Diabetic neuropathy Diabetic retinopathy Advanced age
Learning skill deficiencies	Does patient have deficient reading, writing, or math (numeracy) skills? Is there a language barrier that may affect patient's ability to learn how to administer and self-titrate insulin?

CGM, Continuous glucose monitoring; *SMBG,* self-monitoring of blood glucose.

Adapted with permission from Unger J. *Diabetes management in primary care.* 2nd ed. Philadelphia: Lippincott, Williams and Wilkins, 2012.

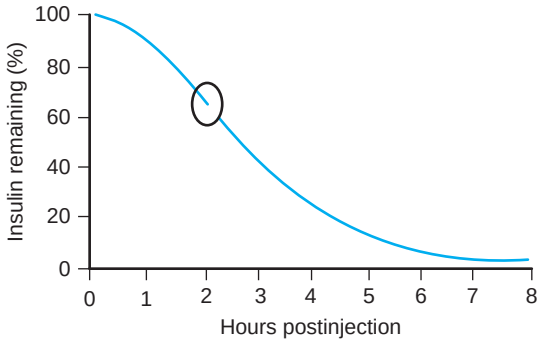

Figure 34-3 Insulin disappearance curve. This graph demonstrates the amount of insulin remaining in the subcutaneous depot over time after a subcutaneous injection (insulin on board). After 2 hours *(circle)*, 64% of the original dose remains in the depot waiting to act. Thus, if 10 units of insulin are given at 10:00 AM, 6 units remain as active drug at noon. The glucose-lowering effects of rapid-acting analogs persist for up to 6 hours after a subcutaneous injection. If a patient gives a correction dose of insulin before the insulin from the previous injection is completely absorbed (a practice known as "insulin stacking"), hypoglycemia is likely to occur. For example, if the blood glucose level is 200 mg/dL at noon and the patient injects an additional 6 units for lunchtime, the subcutaneous depot has now been increased to 12 units. Patients should always calculate insulin on board from the previous injection before injecting supplemental insulin. Insulin stacking is a major cause of hypoglycemia and can easily be avoided. (Adapted with permission from Unger J. *Diabetes management in primary care.* 2nd ed. Philadelphia: Lippincott, Williams and Wilkins; 2012.)

glucose levels) becomes the initial point of intercession. The goal is to achieve a physiological Δ (0-50 mg/dL) for the meal. For example, if the pre-breakfast glucose is 100 mg/dL and the 2-hour postprandial glucose after breakfast is 142 mg/dL, the breakfast Δ = 142 – 100, or 42 mg/dL. Patients with A1C levels above 12% may require immediate initiation of a basal-bolus regimen to reduce postprandial hyperglycemia after all meals.

Structured SMBG also allows patients to identify impending hypoglycemia. Any negative Δ (difference between premeal and 2-hour postprandial glucose resulting in a negative value) would predict a high risk of impending hypoglycemia. For example, if a patient has a premeal glucose level of 187 mg/dL and a 2-hour postprandial glucose level of 100 mg/dL after taking 10 units of insulin, one could predict impending hypoglycemia based on the Δ of −87 mg/dL. If the patient received two 10 units of insulin 2 hours before eating, he or she would be at risk for impending hypoglycemia (Figure 34-3). Calculating Δ values from structured SMBG can also help patients adjust their baseline doses of prandial insulin based on glycemic patterns that become apparent over several days. Table 34-12 lists the causes of low and elevated Δ values.

After a basal-plus or basal-bolus insulin regimen is initiated, a repeat A1C should be obtained to determine if the patient is beginning to trend toward the prescribed glycemic target. Insulin therapy may be intensified based on the patient's A1C level and structured SMBG results.

The initial dose of any prandial rapid-acting insulin can be approximated as 0.1 unit/kg of body weight per meal. Thus, a 100-kg person would require 10 units of rapid-acting insulin, which would be injected 15 minutes before eating. If the 2-hour postprandial glucose is 0 to 50 mg/dL, the correct amount of insulin was given to cover the

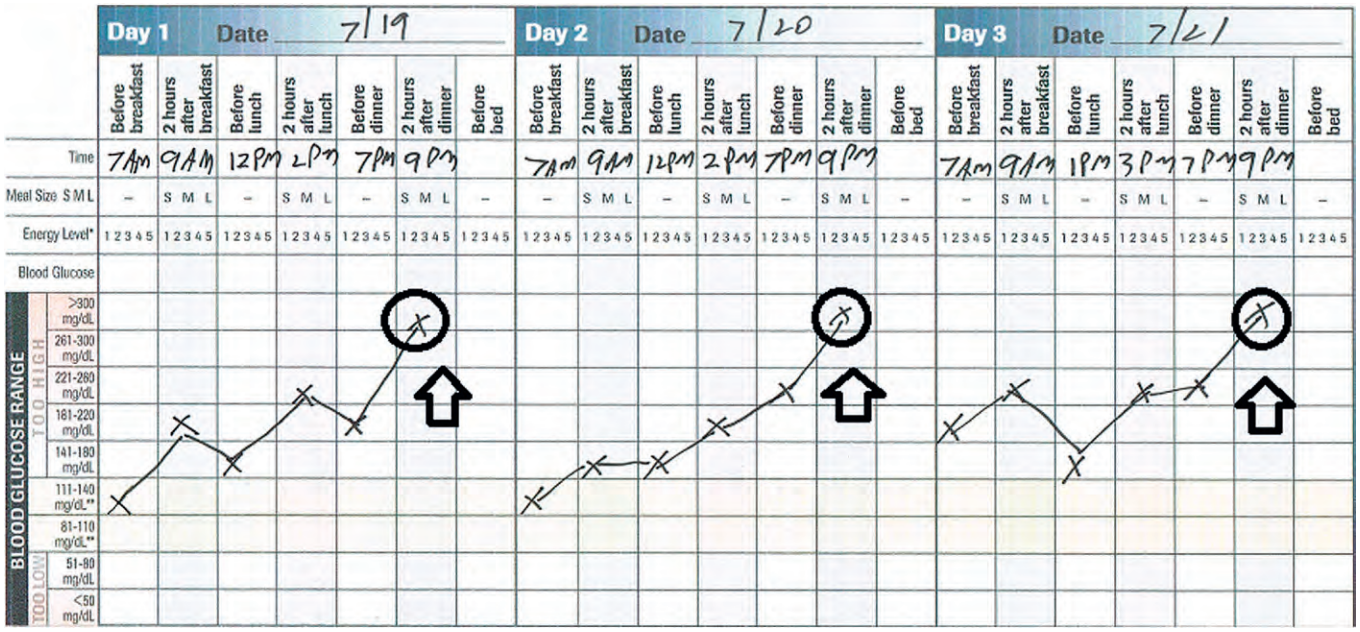

Figure 34-4 Insulin initiation and intensification for patients with advanced type 2 diabetes mellitus (T2DM). *Although any meal may be targeted for rapid-acting insulin intensification, structured self-monitoring of blood glucose should be performed before and 2 hours after each meal for 3 days before a scheduled office visit. The meal that shows the greatest 2-hour postprandial glucose increase (the greatest Δ value) should be targeted for intensification. Note: "Advanced T2DM" refers to patients who have had diabetes for more than 5 years, those whose A1C is greater than 9%, and those who are no longer able to control their glucose with triple combination drug therapy. In this example using the Accu-Check 360 blood glucose analysis system, the patient and his physician were able to determine that the greatest rise in prandial glucose values occurred consistently with dinner. Therefore, basal-plus insulin therapy was initiated, targeting the postprandial excursions at dinner.

carbohydrate content of that meal. However, if the 2-hour postprandial glucose level is consistently above 50 mg/dL, the patient can adjust the mealtime dose of insulin by 1 unit/day until the Δ target is achieved. Figure 34-4 summarizes a popular approach to initiating basal-bolus therapy in the primary care setting. The keys to successful initiation of insulin are summarized in Table 34-20.

PREMIXED INSULIN FORMULATIONS

Premixed preparations combine rapid-acting (prandial) and long-duration (basal) insulins in a single vial or pen injector. Using these fixed-dose insulins can reduce dosing errors that may occur when patients attempt to mix neutral protamine Hagedorn (NPH) and regular insulin in the same syringe. Such formulations are also helpful in other situations. For example, when combining NPH with a rapid-acting analog, the injection must be made immediately to avoid alteration in the glucose-lowering effects of the analog. Patients with visual impairments may have a family member preload their rapid- and intermediate-acting insulin into syringes for use later in the day. However, this may result in absorption variability and hypoglycemia. By contrast, using premixed insulin preparations is simple, user friendly, and more physiological than NPH-plus-regular-insulin injections.

The human premixed insulins (Humulin 50/50, Humulin 70/30, and Novolin 70/30) combine regular and NPH insulin in a single dose. Thirty units of 50/50 insulin would consist of 15 units of regular plus 15 units of NPH. The 70/30 preparations consist of 70% NPH and 30% regular insulin. When used, these insulins must be injected at least 30 minutes before a meal.

Analog premixed insulins (lispro mix 75/25, lispro mix 50/50, and biaspart mix 70/30), unlike human mixed insulins, consist of a set percentage of rapid-acting insulin (either lispro or aspart) plus the rapid-acting insulin combined with protamine, which delays the absorption of that insulin component. By prolonging the duration of action of a percentage of the aspart or lispro within the mixed formulation, protamine improves the glucodynamic effect of the insulin. Patients using a mixed insulin would receive the benefits of a basal and a bolus insulin in a single injection. Thus, a 20-unit dose of lispro 75/25 would contain 5 units of lispro plus 15 units of lispro plus protamine. The analog premixed insulins should be injected 15 minutes before eating to minimize postprandial glycemic excursions.

Although less expensive than the analog premixed formulations, human premixed insulins are less effective at minimizing postprandial glycemic excursions. Using premixed analogs can result in hypoglycemia; however, the incidence of severe hypoglycemia appears to be slightly higher for individuals using human premixed formulations (2%-14% of patients) versus those using premixed analogs (2%-8% of patients).

Premixed insulin analogs might be useful for patients who have a baseline A1C between 8.5% and 10%. Other candidates who might be successful users of premixed analogs include those who eat three meals daily and adhere to a regular schedule for work and physical activity. Another advantage of premixed analogs is that patients receive two insulins for a single insurance copayment.

Table 34-20 Keys to Successful Insulin Initiation in Patients with Type 2 Diabetes Mellitus

Suggest that insulin will help patients achieve their individualized fasting, postprandial, and A1C targets in a timely, safe, and efficient manner.
Provide each patient with a written, individualized treatment plan for insulin intensification.
Use insulin pens or disposable pumps rather than syringes and vials; this may improve dosing accuracy and adherence.
Teach patients how to proactively identify impending hypoglycemia using structured SMBG.
Patients should always be allowed to titrate their basal and prandial insulin doses with prescribed guidance and tutorials from their clinician.
Use insulin analogs; regular human insulin increases the risk of hypoglycemia.
Explain the differences between "basal" and "bolus" insulin to patients to minimize dosing errors.
When adding a GLP-1 receptor agonist to basal insulin, consider reducing the dose of the basal insulin by 20%.
Patients with renal insufficiency should reduce their insulin doses by 10% and monitor their glucose levels carefully because insulin is secreted in the urine. Renal insufficiency may increase circulating insulin levels and increase the risk for hypoglycemia.
To reduce weight gain when insulin is initiated, consider discontinuing any thiazolidinedione, sulfonylurea, or glitinides. Agents that may be continued safely after initiating insulin include metformin, bromocriptine, SGLT2 inhibitors, α-glucosidase inhibitors, DPP-4 inhibitors, and GLP-1 receptor agonists.
Some patients may be able to discontinue insulin if their doses are relatively low (<20 units/day), and they attain an A1C <7.5%. Thus, initiating insulin does not always mean that the patient will be on insulin forever.
Patients must be instructed about how to inject insulin properly. Also, be sure to discuss the proper timing of basal and prandial insulin administration with each patient.
Patients who are shift workers should consider using an insulin pump (continuous subcutaneous insulin infusion) to improve their glucose levels.
Patients with high A1C levels (>10%) do not feel well after eating. This is because their postprandial glucose levels go from bad to worse. After initiating insulin, their symptoms of fatigue and sluggishness should improve dramatically, motivating them to intensify their insulin therapy, if necessary.

DPP-4, Dipeptidyl peptidase-4; *GLP-1,* glucagon-like peptide 1; *SGLT2,* sodium–glucose co-transporter 2; *SMBG,* self-monitoring of blood glucose.

The initiation and titration of premixed insulins has proven successful in allowing patients to achieve their glycemic targets. In a 48-week, multicenter, open-label trial, patients with T2DM and who were not achieving targets on oral agents with or without once-daily basal insulin were placed on premixed biaspart (70/30) in three phases. In phase 1, patients initiated treatment with the premixed formulation once before supper. The dosing frequency was increased to twice daily in phase 2 and to three times daily in phase 3 at 16 and 32 weeks, respectively, if patients did not achieve an A1C of less than 6.5%. Patients reached the end of their participation in the study when they achieved an A1C of 6.5% or less or at 48 weeks, whichever came first. At the end of the trial, 77% of patients had achieved A1C levels of less than 7.0%, and 60% of patients attained an A1C level of 6.5% or less through dosing once, twice, or three times with premixed biaspart (Garber et al., 2006).

Whether treatment-naive patients should begin treatment with basal insulin or a premixed insulin analog was the primary study question of the Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs [INITIATE] trial (Raskin et al., 2004). A total of 233 patients with poorly controlled diabetes on oral agents who had a baseline A1C greater than 8% were randomized to take either insulin glargine or premixed biaspart (70/30) for 28 weeks. At the conclusion of the study, 66% of patients taking premixed biaspart reached the recommended ADA target A1C of less than 7% compared with 40% of those taking glargine. As expected, postprandial glycemic excursions for the biaspart group were approximately 25% lower than for patients using glargine. Minor hypoglycemia occurred more commonly in patients taking the premixed insulin, but no episodes of severe hypoglycemia were recorded during the trial.

Treatment of patients with T2DM should no longer be protocol driven. The ACCORD trial demonstrated that intensive therapy can be used successfully to reduce A1C to less than 6.5% in patients with T2DM. Unfortunately, the all-cause mortality rate in ACCORD was 22% in intensively managed patients (ACCORD Study Group, 2008). Not all patients are at risk if ambitiously treated, however. In fact, the patients who were able to lower their A1C to below 6.5% within 4 months of randomization did not demonstrate in increase in all-cause mortality. Those who were unable to achieve their targeted goal by intensification appeared to have elevated postprandial glucose levels that were more refractory to treatment. These individuals also had longer disease durations and were at higher risk of experiencing fatal arrhythmias caused by severe hypoglycemia (Riddle et al., 2010).

Thus, metabolic targets for diabetes must be individualized based on the patient's age, disease duration, number and severity of comorbidities, history of hypoglycemia awareness autonomic failure, ability to participate in self-diabetes management, and life expectancy. Most newly diagnosed patients with diabetes should attempt to lower their A1C to 6.5% or less. Pharmacotherapy choices should be selected based on their ability to correct and reverse the metabolic defects associated with T2DM and insulin resistance. Simply attempting to target a given glycemic parameter is no longer a safe or acceptable practice when managing patients with either T1DM or T2DM.

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus accounts for 5% to 10% of all individuals diagnosed with diabetes and results from a cellular-mediated autoimmune destruction of the pancreatic β cells. Markers of immune destruction of β cells include islet cell autoantibodies (ICAs), autoantibodies to insulin (IAAs), autoantibodies to glutamic acid decarboxylase (GAD65), antibodies to an insulinoma-associated antigen-2 (ICA512), and autoantibodies to the tyrosine phosphatases (IA-2 and IA-2β) (ADA, 2012). One or more of the autoantibodies are present in 85% to 90% of individuals who initially experience fasting hyperglycemia.

The rate of β-cell destruction in T1DM varies. Whereas infants and children tend to demonstrate rapid β-cell death, adults typically present with a lengthy prodromal phase leading to latent autoimmune diabetes of adulthood (LADA)

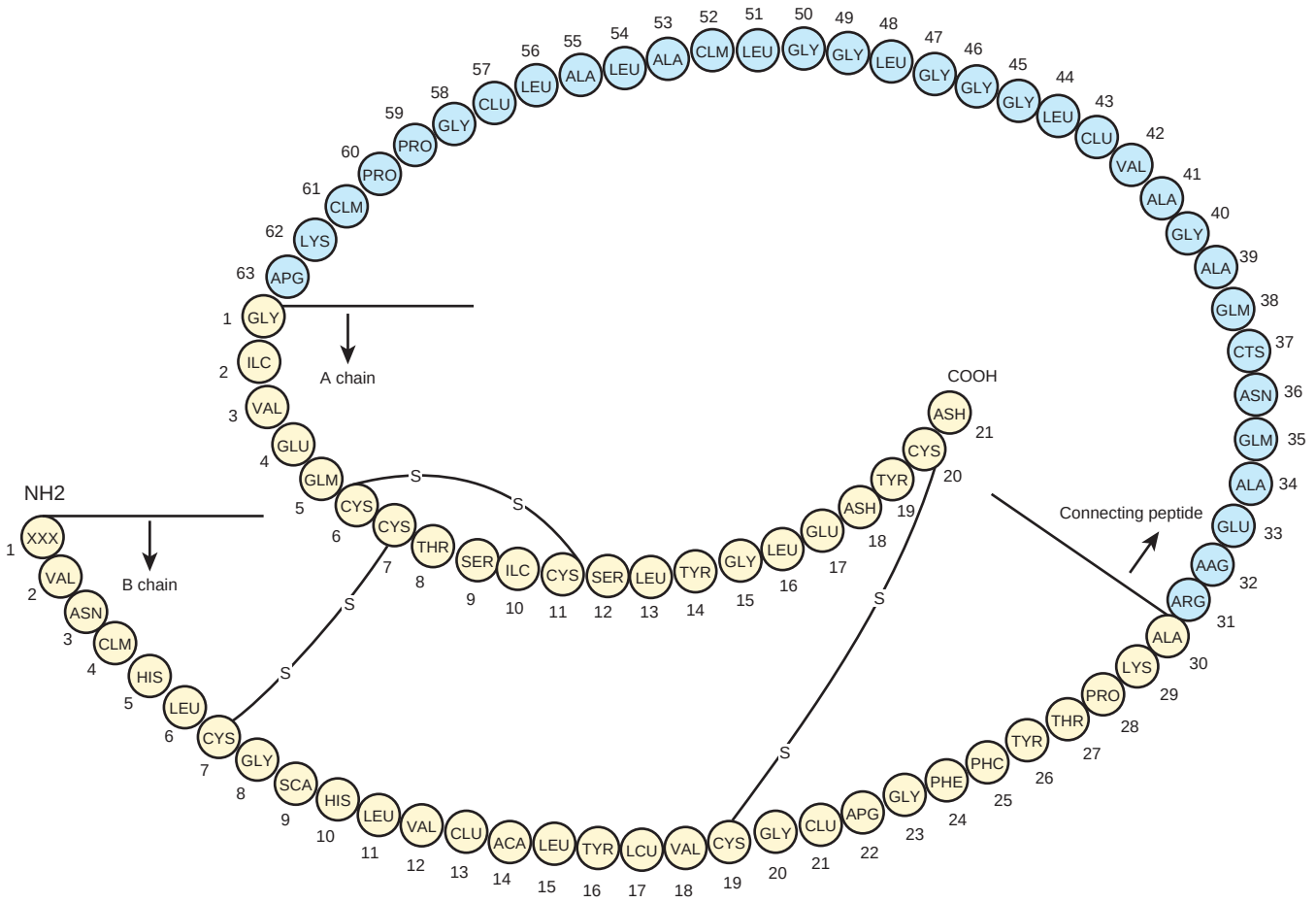

Figure 34-5 Structure of human insulin. The precursor of insulin, proinsulin, is produced within the endoplasmic reticulum of the pancreatic β cells. Proinsulin is then transported to the Golgi apparatus and packaged into secretory vesicles. The C-peptide chain is released from the center of the proinsulin sequence while the two disulfide bonds remain intact. One C-peptide molecule is formed with each insulin molecule. Therefore, C-peptide levels can serve as an accurate measure of endogenous insulin production. C-peptide levels in euglycemic individuals range from 0.5 to 2.0 ng/mL. Patients with type 1 diabetes mellitus are deficient in C-peptide. (Adapted with permission from Unger J. *Diabetes management in primary care.* 2nd ed. Philadelphia: Lippincott, Williams and Wilkins; 2012.)

(Unger, 2008a). Some children and adolescents may present with DKA as the first manifestation of the disease. Others have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia or DKA in the presence of infection or other stress. Adults may retain residual β-cell function (remaining C-peptide positive; Figure 34-5) that is sufficient to prevent DKA for many years. Residual β-cell function detected 3 to 6 years after the onset of T1DM has also been associated with a lower risk of hypoglycemia, reduced exogenous insulin requirement, and improved glycemic control (Sorensen et al., 2013).

Patients with near-complete insulin deficiency who remain antibody negative are classified as having "type 1B diabetes" (Notkins and Lernmark, 2001). Most patients with type 1B diabetes are of African or Asian ancestry.

Patients with T1DM are prone to other autoimmune disorders such as autoimmune thyroid disease (15%-30%), celiac disease (4%-9%), and Addison disease (0.5%) (Unger, 2012e). Assays for thyroid peroxidase autoantibodies (for autoimmune thyroid disease), tissue transglutaminase autoantibodies (for celiac disease), and 21-hydroxylase autoantibodies (for Addison disease) may be used to screen asymptomatic patients to identify those at high risk for clinical progression to these conditions. Thirty-three percent of patients with T1DM screen positive for at least one additional organ-specific autoantibody when initially diagnosed with diabetes, and 19% have evidence of clinical disease. Given the high preponderance of these antibodies at the onset of T1DM, screening for coexisting autoimmune disorders appears to be warranted (Triolo et al., 2011).

To date, no intervention has been developed that can unequivocally prevent the development of T1DM or arrest the progression of immune system destruction of β cells after diagnosis. Although some promising studies in the area of diabetes prevention and reversal have given the field much encouragement, most of these efforts are unfolding at large academic or research-focused medical centers. Nonetheless, family physicians play a vital role in working with patients who are at high risk for developing T1DM. In families with established T1DM, all first-degree relatives, including the parents of the patient (if they are younger than 45 years of age), are at increased risk for T1DM and should be counseled about this risk. Identical twins are at the greatest risk. Second- and third-degree relatives of patients with T1DM are also at heightened risk if they are younger than 21 years of age.

Table 34-21 Features of Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, and Latent Autoimmune Diabetes of Adulthood

	Features					
Condition	**DKA**	**Cardiovascular Complications**	**Microvascular Complications***	**Pathophysiology**	**Autoantibodies**	**Insulin Requirements**
T1DM	Develops rapidly unless patient receives insulin therapy	Increased risk of cardiovascular morbidity and mortality related to stroke, acute coronary event, or coronary revascularization; high incidence of cardiovascular complications compared with euglycemic people, especially in women	Increased risk	Autoimmune destruction of pancreatic β cells	Patients typically test positive for ≥2 autoantibodies	Insulin required at diagnosis
LADA	Absent at diagnosis but may develop with severe insulinopenia	Risk is two to four times higher than in euglycemic people	Increased risk	Latent autoimmune destruction of pancreatic β cells	Glutamic acid decarboxylase autoantibodies most common; islet cell antibodies less common Patients typically test positive for only one autoantibody	Insulin therapy is ultimately necessary; may be considered if autoantibodies are identified
T2DM	Usually absent	Risk is two to four times higher than in euglycemic people	Increased risk	Peripheral insulin resistance; reduced pancreatic β-cell mass and function; reduced insulin	Usually absent	Usually needed late in the disease course when the remaining β-cell mass and function can no longer support acceptable glycemic control with oral agents or incretin mimetics

*Retinopathy, nephropathy, and neuropathy
LADA, Latent autoimmune diabetes of adulthood; *T1DM,* type 1 diabetes mellitus; *T2DM,* type 2 diabetes mellitus.
Unger J. Diagnosing and managing latent autoimmune diabetes in adults. *Pract Diabetol.* 21:32-37, 2008.

After being apprised of their diabetes risk, such individuals should be made aware of T1DM screening and intervention studies such as the National Institutes of Health's T1DM TrialNet (http://www.diabetestrialnet.org). The advantages of screening for T1DM risk through such research-oriented programs include state-of-the-art antibody determinations in specialized research laboratories, a superb follow-up and support network of T1DM specialists, protection of laboratory data from insurance carriers, and the opportunity to participate in further clinical research studies aimed at diabetes prevention. Participating in a research study incurs no cost to patients or their insurance companies.

Early vitamin D supplementation may protect against T1DM progression, although the exact mechanism is uncertain. Vitamin D is a potent modulator of the immune system and is involved in regulating cell proliferation and differentiation (Zella and DeLuca, 2003). A meta-analysis of data from five observational studies recently indicated that children supplemented with vitamin D had a 29% reduction in T1DM risk compared with their unsupplemented peers (Zipitis and Akobeng, 2008).

LATENT AUTOIMMUNE DIABETES IN ADULTS

Latent autoimmune diabetes in adults is a slowly progressive form of autoimmune diabetes characterized by older age at diagnosis, the presence of pancreatic autoantibodies, and the lack of an absolute insulin requirement at diagnosis. Although patients with LADA present with more preserved β-cell function than those with classic T1DM, they tend to have a rapid and progressive loss of β-cell function necessitating intensive insulin intervention. Approximately 10% of all patients diagnosed with T2DM actually have LADA (Isomaa et al., 1999). Table 34-21 compares the characteristics of T1DM, T2DM, and LADA.

Although the exact pathogenesis of LADA is unclear, the underlying immune-mediated destruction of β cells in patients with this form of the disease leads to insulin dependency more rapidly than in patients with T2DM. Protective alleles appear to delay absolute exogenous insulin dependency in people with LADA compared with those with T1DM.

Suspicion of LADA should be heightened in patients with coexisting autoimmune disorders such as hypothyroidism,

who are not excessively overweight, and who have deteriorating glycemic control despite intensification of oral therapies and the use of incretin mimetics. Physicians may consider GAD65 testing to determine whether LADA is present.

Because of the ambiguous pathophysiology and clinical characteristics of LADA, no specific guidelines have been established for its treatment. Nevertheless, theoretical advantages of intensive insulin therapy exist. Eighteen years after the DCCT, a follow-up study showed that early control of diabetes over 6.5 years seems to provide continued protection against micro- and macrovascular complications (DCCT Research Group, 1993; DCCT/EDIC Research Group, 2005). This result occurred despite the fact that patients in the DCCT who received intensive treatment had deteriorating A1C levels over time, but those in the conventional treatment group showed improvement upon completion of this landmark study. Early stabilization of glycemic control in patients with T1DM is postulated to establish "metabolic memory," which theoretically protects against long-term complications.

PATHOGENESIS OF TYPE 1 DIABETES MELLITUS

Type 1 diabetes mellitus occurs in individuals in whom genetic susceptibility outweighs genetic protection. Distinctive environmental triggers play a supporting role in provoking a cellular-mediated autoimmune process directed to one or more β-cell proteins (autoantigens). As islet cell destruction occurs, autoantibodies are delivered into the pancreatic lymph nodes, where destructive T-effector cells are produced and outnumber the stabilizing T-regulatory cells. Initially, the decline in β-cell function and loss of β-cell mass present clinically as loss of first-phase insulin response to an intravenous glucose challenge. Over time, patients progress through stages of "dysglycemia" (glucose values >200 mg/dL at 30, 60, or 90 minutes during an oral glucose tolerance test). Ultimately, the clinical syndrome of T1DM becomes evident when the majority of β-cell function has been lost and most β cells have been destroyed. At this juncture, frank hyperglycemia supervenes. To date, no intervention has been developed that can unequivocally prevent the development of T1DM or arrest the progression of immune system destruction of β cells after diagnosis, although some promising studies have given the field much encouragement (Unger, 2012e).

OUTPATIENT MANAGEMENT OF ADULTS WITH TYPE 1 DIABETES MELLITUS

The ultimate goal of insulin replacement therapy is to mimic the normal insulin response to hyperglycemia in both the fasting and postprandial states. Physiological insulin replacement regimens include the use of basal-bolus insulin preparations administered in a multiple daily injection (MDI) regimen or through continuous subcutaneous insulin infusion (CSII; insulin pump therapy). Nonphysiologic regimens include NPH insulin with or without a rapid-acting insulin, premixed insulin analogs, or analog basal insulin therapy alone given once or twice daily. Such regimens fail to mimic the normal glucose-stimulated insulin response of pancreatic β cells. Physiological insulin therapies require individualization and titration based on the factors shown in Table 34-19.

Insulin Analog Formulations

Basal Insulin Analogs. The two available basal analogs include glargine and detemir. Glargine provides glycemic control that is at least comparable with NPH in adults, adolescents, and children. However, the risks of mild and severe episodes of hypoglycemia are significantly reduced with glargine compared with NPH use in adults. Combining glargine with a rapid-acting insulin analog as part of an MDI regimen provides benefits over the use of NPH plus regular human insulin (Garg et al., 2011).

The absence of clear peaks in the time-action profiles of glargine and detemir contributes to the lower risk of hypoglycemia with these analogs compared with NPH. In addition, the analogs demonstrate less variability in absorption compared with NPH, suggesting that the analog formulations have a more predictable glucose-lowering effect than NPH in T1DM (Heise et al., 2004).

Rapid-Acting Insulin Analogs. Rapid-acting insulin analogs begin to exhibit their glucose-lowering effects within 10 to 15 minutes after an injection compared with the 30- to 60-minute onset of action of regular human insulin. The three available rapid-acting insulin analogs are lispro, aspart, and glulisine. Aspart and glulisine have also been approved for injection immediately after a meal. Postprandial administration can be useful for patients who forget to take their insulin before eating. Pediatric and elderly patients whose food consumption and mealtimes are unpredictable may also bolus after eating.

Table 34-22 lists the pharmacologic characteristics of commercially available insulin preparations, as well as an investigational long-acting basal insulin (degludec), which is now in phase 3 clinical trials.

INITIATING AND INTENSIFYING PHYSIOLOGICAL INSULIN THERAPY IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

Findings from large RCTS clearly demonstrate that early and aggressive management of glycemia significantly decreases the development and progression of both micro- and macrovascular complications of diabetes (DCCT Research Group, 1993; DCCT/EDCIC Research Group, 2005). Unfortunately, intensification of therapy and improved glycemic control are often associated with an increased frequency of severe hypoglycemia (DCCT Research Group, 1993). Thus, the rate-limiting step to diabetes intensification remains fear on the part of patients or providers of inducing iatrogenic hypoglycemia. Patients must receive education about how to avoid, recognize, and treat hypoglycemia. If necessary, clinicians should consider the use of a continuous glucose monitoring (CGM) devices, which have alarms to help patients avoid hypoglycemia. Table 34-23 lists self-management goals for patients who are prescribed basal-bolus insulin therapy.

Patients with T1DM must make many therapeutic decisions, most often without physician guidance, on a daily basis. Amazingly, most patients become quite adept at adjusting their insulin doses according to their specific and

Table 34-22 Pharmacologic Characteristics of Commercially Available Insulin Preparations

Insulin Preparations	Onset of Action	Peak Action (hr)	Duration of Action (hr)
HUMAN INSULINS			
Prandial			
Regular	30-60 min	2-4	6-8
Intermediate Acting			
NPH	1-4 hours	6-10	10-16
Premixed			
70/30 (70% NPH, 30% regular)	0.5-1.0 hr	First peak 2-3 hr; second peak several hours later	10-16
50/50 (50% NPH, 50% regular)	0.5-1.0 hr	First peak 2-3 hours; second peak several hours later	10-16
INSULIN ANALOGS			
Basal			
Glargine	1-4 hr	No pronounced peak	24 (terminal half-life = 12.5 hr)
Detemir	1-4 hr	No pronounced peak	20-24
Degludec*	—	No peak	>24 hr (terminal half-life = 25 hr)
IDegAsp* (degludec + aspart)	10 min†	No peak	>24 hr (equal to degludec)
PRANDIAL			
Lispro/aspart/glulisine	5-15 min	1-2	3-4
Premixed			
Lispro mix 75/25 (75% protamine lispro/25% lispro)	15 min	0.5-1.2	10-16
BiAsp 70/30 (70% protamine aspart/30% aspart)	15 min	0.5-1.2	10-16
Lispro mix 50/50	15 min	0.5-1.2	10-16

*These insulins are in phase 3b clinical trials and have been submitted for review to the Food and Drug Administration.
†Degludec has a flat profile under steady-state conditions. There is no peak. Therefore, "time to peak action" and onset of action become irrelevant. Steady state for degludec is achieved on the third day of treatment. The effect of the previous injection will cover the time between injection and onset of action of the subsequent injection. The duration of action is dose dependent. Higher doses increase the duration of action for any insulin. The terminal half-life of insulin degludec is 25 hours compared with 12.5 hours for insulin glargine. There are no published data regarding the duration of action of insulin degludec. However, the end of action (end of action is defined as blood glucose levels >150 mg/dL) was not reached by 42 hours after the conclusion of glucose clamping for subjects receiving either 0.6 or 0.8 units/kg. The duration of action of IDegAsp is determined by the degludec component. The onset of action of IDegAsp is based on the aspart component. BiAsp has an onset of action of 10 minutes and a duration of action of 1 to 3 hours.
NPH, Neutral protamine Hagedorn.
References: Aventis, 2003; Garg and Ulrich, 2006; Heise et al., 2011; Hirsch, 2005; Lepore et al., 2000; Nosek et al., 2011; Novo Nordisk, 2005.

Table 34-23 Self-Management Goals for Patients Using Basal-Bolus Insulin Therapy

- Prescribe a protocol that will allow patients to successfully and safely achieve the ADA's fasting blood glucose target of 90-130 mg/dL.
- Target 2-hour postprandial blood glucose levels <180 mg/dL.
- Minimize the rise in postprandial blood glucose levels from premeal baseline levels of ≤50 mg/dL.
- Minimize the risk of developing hypoglycemia by instructing patients about appropriate pattern glucose testing and means by which hypoglycemia may be predicted and treated proactively.
- Allow patients to self-titrate their basal and prandial insulin doses based on specified treatment targets (fasting and postprandial glucose excursions).
- Encourage use of certified diabetes educators and registered dietitians to assist patients in learning and appropriately incorporating their treatment regimens into their active lifestyles.
- Individualize insulin regimens to include considerations for exercise, travel, and sleep.
- Recognize and effectively manage patients with mental illness and eating disorders.
- Individualize treatment based on cultural, religious, and personal preferences.
- Periodically review injection and SMBG technique to ensure that these basic skills are being performed properly.

ADA, American Diabetes Association; *SMBG,* self-monitoring of blood glucose.

immediate metabolic requirements. On occasion, patients may bolus inappropriate doses of insulin. In such cases, clinicians should never rebuke patients for missing their fasting or postprandial glucose targets. After all, they are doing the best they can with the insulin dosing resources provided by their health care providers.

The following steps may be used to safely and effectively initiate and titrate basal-bolus insulin for insulin-requiring patients (Unger, 2007):

Step 1. Determine the total daily dose (TDD) of insulin. The TDD is equal to the weight in kg × 0.7. For example, a 70-kg patient would require a total of $70 \times 0.7 = 49$ units of insulin daily.

Step 2. Determine the starting dose of basal insulin analog (glargine or detemir) and rapid-acting insulin (aspart, lispro, or glulisine).

$$\text{Basal insulin dose/24 hours} = 50\% \text{ of TDD}$$

$$\text{Bolus insulin dose/24 hours} = 50\% \text{ of TDD}$$

Basal insulin minimizes the effects of hepatic glucose production, thus keeping blood glucose levels regulated in the fasting state. The basal insulin requirement is equal to 50% of the TDD. Thus, a patient requiring 50 units/day of insulin would require approximately 25 units of

basal insulin. The remaining 50% would be dedicated to bolus insulin.

These percentages may vary from patient to patient. Some individuals may require a 40/60 split favoring bolus insulin. Basal insulin should be injected at a consistent time each day or night because its maximum duration of action is 24 hours. After it is initiated, the basal insulin can be titrated by increasing the dose by 1 unit/day until fasting blood glucose is less than 100 mg/dL (Harris et al., 2008).

Step 3. Establish a prandial dosing regimen.

A. Determine baseline prandial insulin dosage:

Dose of prandial insulin = 0.1 units/kg/meal (e.g., a 70-kg patient would require 70 × 0.1 units = 7 units of rapid-acting insulin per meal)

B. Establish the lag time for insulin injection:
Insulin should be injected 15 minutes before a meal unless the blood glucose level before eating is less than 80 mg/dL, in which case insulin should be injected at the onset of the meal.

C. Allow the patient to adjust the insulin dose based on the size of the meal (Table 34-24). For example, a patient with a baseline prescribed prandial insulin dose of 7 units plans to eat a Thanksgiving-sized feast. The dose of insulin would be 7 + 3 = 10 units injected 15 minutes before eating. The baseline prandial insulin dose can be further adjusted based on structured glucose testing (Table 34-25).

Table 34-24 Prandial Dose Adjustments of Rapid-Acting Insulin

Meal Size	Prandial Insulin Dose Adjustment
Standard meal	No change
Very large meal with dessert	+3 units from baseline dose
Large meal without dessert	+1 to 2 units from baseline dose
Smaller than usual meal	−1 to 2 units from baseline dose

D. Adjust the patient's initial baseline dose of insulin periodically based on the results of structured SMBG.

Step 4: Fine tune basal-bolus doses of insulin based on structured SMBG.

- Perform SMBG before eating and 2 hours after each meal.
- If 2-hour postprandial glucose is consistently more than 50 mg/dL above baseline for a given meal, increase insulin dose by 1 to 2 units. The target 2-hour postprandial Δ is 0 to 50 mg/dL (see Table 34-12).
- Any negative Δ (e.g., −25 mg/dL from baseline) predicts hypoglycemia. Blood glucose levels must be rechecked in 1 hour to monitor for hypoglycemia.
- A pattern of negative Δ values for a given meal suggests a mismatch between insulin dosing and carbohydrate intake for that meal. Reduce insulin dose by 1 to 2 units.

Table 34-25 shows examples of how structured glucose testing may be used to fine tune prandial insulin regimens.

Step 5: Establish an insulin sensitivity factor to determine correction doses for premeal hyperglycemia.

- Correction doses may be used to correct an elevated blood glucose value before eating.
- Patients can safely correct if their premeal glucose level is greater than 180 mg/dL.
- Postcorrection blood glucose target should always be 150 mg/dL (to avoid overshooting that conservative goal and inducing hypoglycemia).
- Insulin sensitivity factor is the number of mg/dL that 1 unit of insulin is expected to lower blood glucose and is based on the "rule of 1800."

1800/TDD = Expected drop in blood glucose from 1 unit of insulin. Example: If TDD is 70 units, the insulin sensitivity factor would be:

1800/70 = 25.7 (Round off to 25.)

Thus, if the premeal blood glucose is 200 mg/dL and the target blood glucose is 150 mg/dL, the patient would give

Table 34-25 Example of Structured Self-Monitoring of Blood Glucose for Patients with Type 1 Diabetes Mellitus

Date	Pre-Lunch Glucose (mg/dL)	2-Hour Post-Lunch Glucose (mg/dL)	Δ (Difference between Baseline Glucose and 2-Hour Postmeal Glucose)	Reasons for Δ Being <0 (a "Negative Δ") (Could Indicate Impending Hypoglycemia; List Actions Taken for Hypoglycemia)	Reasons for Δ Being >50 mg/dL (List Corrective Actions)
2/13	125	225	+100	—	Bolus given at meal time rather than 15 minute before eating Mismatch of insulin to carbohydrate (ate dessert); will give 2 units for dessert next time
2/14	110	154	44 (at target)	—	—
2/15	227	117	−110	Overcorrected on premeal insulin dose; became hypoglycemic 3 hours after eating but consumed 15 g of carbohydrate	
2/16	153	169	+16	Perfect	No need for adjustments for this type of food
3/17 3/18 3/19	125 100 135	200 190 235	+75 +90 +100	Stopped daily afternoon workouts; caring for ailing mother-in-law	Advised to increase baseline lunchtime prandial insulin dose by 2 units

a correction dose of 2 units (to correct for 50 mg/dL above target) in addition to the baseline prandial insulin dose at that particular meal. A patient who normally boluses 7 units before eating and has a 200 mg/dL premeal glucose value would add 2 units to the prandial dose for a total bolus dose of 7 + 2 = 9 units before eating.

- Patients who plan to eat a large meal may adjust their mealtime dose further according to the options mentioned in Table 34-24.
- SMBG should be performed 2 hours after eating to ensure that the correction dose did not cause glucose levels to trend toward hypoglycemia as a result of overcorrection.

Multiple daily injections should be initiated and maintained with the use of insulin pens rather than syringes and vials. Insulin pens allow for accuracy, portability, flexibility, and ease of use. Insulin pens typically do not need refrigeration, which may provide for additional patient adherence to therapy over vial-and-syringe insulin delivery. Patients must be familiar with the nuances of using each type of pen delivery device. Most important, errors in insulin delivery can be avoided if patients make certain that they are giving the appropriate formulation of insulin for basal or prandial coverage.

Patients whose A1C levels rise despite being provided adequate dosing protocols for a basal-bolus regimen may be nonadherent to their prescribed insulin regimen. One study found that 64% of T1DM patients were incorrectly assessing their prandial insulin requirements (Ahola et al., 2010). Barriers to insulin intensification in T1DM include fear of hypoglycemia, weight gain, inconvenient dosing protocols, and confusion about appropriate dosing of mealtime insulin (Cavan et al., 2012). Table 34-26 lists the advantages of insulin pens over syringes and vials (Asamoah, 2008).

Table 34-26 Advantages of Insulin Pen Delivery Systems versus Syringes and Vials

Clinicians can teach pen use to patients in <3 min on average. There is no need to inconvenience patients by having them learn the technique of insulin injection offsite.
Use of 30- or 31-gauge short needles with pens has significantly reduced the needle phobia that patients have about taking injections. Also, needles are less painful when they do not have to be inserted through the rubber stopper of a vial, which destroys the fine tip needle coating and thus increases injection pain.
Pens are easier then vials and syringes to carry in a pocket or purse.
Pen devices have been shown to be more accurate than syringes for delivering insulin doses ≤5 units, so they may benefit children and adolescents, who usually require smaller doses (Gnanalingham et al, 1998).
Older patients with diabetes who have comorbidities or disabilities (e.g., visual impairments, tremors, or impaired motor skills) that may exacerbate the difficulties of self-injection and increase the risk of dosing errors often find that pen devices can help to overcome such limitations.
Numerous patient surveys have demonstrated that patients prefer pens over vials and syringes (Asamoah, 2008).

Gnanalingham MG, Newland P, Smith CP. An evaluation of NovoPen, BD-Pen, and syringe devices at small doses of insulin [Abstract P118]. Presented at the British Diabetes Association's Medical and Scientific Section Spring Meeting in Edinburgh, Scotland, March 25-27, 1998; Asamoah E. Insulin pen: the "iPod" for insulin delivery: why pen wins over syringe. *J Diabetes Sci Technol.* 2:292-296, 2008.

INSULIN PUMP THERAPY AND CONTINUOUS GLUCOSE SENSORS

Continuous subcutaneous insulin infusion, also known as insulin pump therapy, allows patients with diabetes to achieve improved glycemic control while using less daily insulin, reducing the likelihood of weight gain and hypoglycemia, and limiting diurnal glycemic variability compared with insulin delivery via vials and syringes or insulin pen devices (Weissberg-Benchell et al., 2003). Because of the lifestyle flexibility that insulin pump users enjoy, quality-of-life assessment scores consistently favor CSII over MDI regimens. Switching from an MDI regimen to CSII will limit the number of short-term complications such as hypoglycemia and DKA, as well as reduce the risk for long-term microvascular complications (Weissberg-Benchell et al., 2003).

Although CSII is certainly the most sophisticated and precise insulin-delivery method currently available, patients who initiate pump therapy must be solidly committed to diabetes self-management. SMBG must be performed six to eight times daily unless patients use concomitant CGM devices. Patients must understand insulin pharmacokinetics, become adept at appropriate dosing and timing of prandial insulin, and be knowledgeable about exercise physiology. Pumps are machines that may fail, malfunction, or even be lost. Therefore, pump users must be trained to fall back to an emergency protocol such as pen or syringe insulin delivery to allow them to control hyperglycemia and minimize the risk of DKA if their pump malfunctions.

Fortunately, the vast majority of insulin pump users are skilled diabetes self-managers who often put clinicians to shame with their disease state knowledge. Because pump users are both challenging and intelligent members of the diabetes community, primary care physicians should learn the basics of pump therapy. Clinicians who feel comfortable intensively managing patients with MDI regimens are also capable of initiating and titrating insulin pump regimens (Unger, 2012b).

Ideally, insulin replacement should mimic the normal glucose and endogenous insulin response to the fasting and prandial states. However, prandial injection therapy, whether given by a syringe or a pen device, cannot provide an exact physiological dose to replicate first- and second-phase insulin secretion. A pen- or syringe-delivered dose of insulin mimics only first-phase (acute) insulin secretion. The bolus dose may not be sufficient to cover a delayed rise in glucose that may occur if the consumed meal is high in fat. Thus, patients may experience an insulin-to-carbohydrate mismatch, resulting in early postabsorptive hypoglycemia followed by an increase in plasma glucose as the rapid-acting insulin analog absorption is mitigated. To address this problem, insulin pumps allow patients to provide a bolus of insulin in percentages over time. For example, 20% of the insulin dose may be bolused immediately, and the remainder can be released as an "extended bolus" over several hours.

A similar problem exists regarding basal insulin delivered via pen or syringe. Giving one dose via pen or syringe assumes that basal insulin requirements will not change during the 24-hour period after the dose is given. However, patients who exercise will have reduced basal insulin requirements. Before patients arise in the morning, their

Table 34-27 Candidates for Continuous Subcutaneous Insulin Infusion Therapy

CSII should be considered for patients who:
- Have frequent hypoglycemia or hypoglycemia unawareness
- Fail to reach goal A1C with MDI insulin regimen
- Exercise regularly
- Experience the dawn phenomenon, which cannot be controlled with a single daily injection of basal insulin
- Travel frequently or are employed in shift work
- Are pregnant or planning for pregnancy
- Are children or adolescents
- Have gastroparesis
- Have a history of frequent DKA
- Experience severe insulin resistance (requiring >250 units of insulin daily)
- Would prefer to use an insulin pump rather than following an MDI regimen
- Are undergoing chemotherapy; glycemic variability may increase cancer-related mortality
- Have multiple micro- and macrovascular complications; hypoglycemia increases mortality in these patients
- Have ESRD
- Are athletes at any level of competition

CSII, Continuous subcutaneous insulin infusion; *DKA,* diabetic ketoacidosis; *ESRD,* end-stage renal failure; *MDI,* multiple daily injection.

basal insulin requirements increase in response to physiological insulin resistance caused by increased production of cortisol and growth hormone (a circumstance known as the "dawn phenomenon"). In the afternoon hours, insulin requirements are typically lower than during the morning and evening hours. Unfortunately, after a pen or syringe injection of basal insulin is given, the drug's influence on basal insulin levels cannot be altered; one cannot turn up or turn down the level of basal insulin injected the evening before in response to exercise or varying degrees of insulin resistance occurring in the 24-hour period after the injection. Insulin pumps address this issue by allowing patients to program multiple basal insulin delivery rates to match their individualized sleep patterns, physical activity, menstrual schedule, medications, and travel plans. (Such a feature is ideal for steroid-dependent patients who experience postprandial hyperglycemia and normal fasting glucose values.)

Thus, CSII allows patients with T1DM or insulin-requiring T2DM to enjoy a flexible lifestyle while avoiding hypoglycemia. By programming changes to both basal and bolus insulin delivery rates, pump users adjust their regimen to closely simulate normal endogenous β-cell insulin secretion.

Insulin pumps have been available since the 1980s, and more than 400,000 pump devices are sold annually worldwide (Unger, 2012b). Table 34-27 lists some of the indications for considering CSII in insulin-requiring patients with diabetes.

Patients may also integrate their CSII regimen with CGM. CGM systems operate by measuring glucose levels in interstitial fluid. The devices consist of three components: a disposable sensor that measures glucose levels, a transmitter that is attached to the sensor, and a receiver that displays and stores glucose information. The information stored in the receiver is then converted into estimated mean values of glucose standardized to capillary blood glucose levels measured during calibration. Using an applicator or self-insertion device, patients insert a thin plastic sensor just under the skin of the abdomen or upper arm. These devices can display real-time glucose values and trends, and some can help patients avoid hyper- and hypoglycemia by sounding an alarm or vibrating when glucose levels rise above or fall below preprogrammed upper and lower thresholds. The receiver can store information for later use, and long-term data can be downloaded to a computer. Real-time trend graphs can be downloaded to a computer or displayed on the pump screen, which can be useful in identifying glycemic trends in response to physical activity, meals, insulin doses, menstruation, illness, or other factors.

The Medtronic MiniMed 530G system integrates CGM with CSII in one device that uses sensor-augmented pump technology. The CGM communicates with the pump and will automatically suspend insulin delivery when glucose values reach a pre-programmed low threshold.

EXERCISE AND TYPE 1 DIABETES MELLITUS MANAGEMENT

During the transition from rest to exercise, skeletal muscles shift from using predominantly FFAs released from adipose tissue to a mixture of muscle triglycerides, muscle glycogen, and glucose derived from glycogenolysis. During the initial stages of moderate exercise, muscle glycogen is the primary energy source. However, as exercise becomes more prolonged, glycogen stores become depleted, requiring the body to rely on circulating FFAs and plasma glucose as fuel sources. During heavy exercise (30-60 minutes at 80% of maximal oxygen uptake), peripheral glucose utilization may be as high as 1 to 1.5 g/min (Wasserman et al., 2002). This source of energy must be continuously replaced at an equal rate to prevent the onset of exercise-induced hypoglycemia.

In euglycemic individuals, plasma glucose levels are sustained during exercise because pancreatic insulin secretion decreases while levels of glucagon, growth hormone, cortisol, and catecholamines increase. Patients with T1DM lack the ability to regulate both endogenous insulin secretion and counterregulatory hormones in response to exercise, making maintenance of physiological fuel regulation nearly impossible. Thus, patients must adjust their carbohydrate consumption and insulin doses, as well as their exercise intensity, mode, and duration, to minimize the risk of hypoglycemia and exercise-induced DKA.

Intensive management of T1DM increases the risk of exercise-induced hypoglycemia. Exercise acutely increases peripheral glucose utilization within skeletal muscles, thus making circulating exogenous insulin "turbo-charged."

Patients with poorly controlled T1DM are at risk for exercise-emergent DKA (Riddell and Perkins, 2006). Prolonged exercise triggers hepatic glucose production. Insulinopenic patients with a baseline plasma glucose level greater than 240 mg/dL experience a rise in plasma glucose levels as exercise intensifies. Low circulating insulin levels cannot suppress hepatic glucose production during exercise. Dehydration combined with an exercise-induced increase in catecholamines will likely hasten the onset of DKA in these individuals (Marliss and Vranik, 2002). Table 34-28 lists suggested practical guidelines to minimize blood

Table 34-28 Suggestions for Minimizing Blood Glucose Excursions before, during, and after Exercise for Patients with Type 1 Diabetes Mellitus

Time Period	Recommendations
Before exercise	Determine the timing, mode (aerobic vs. resistance training), and intensity of exercise to be performed. Perform SMBG before exercising. A safe target blood glucose before moderate exercise is 120-180 mg/dL. If blood glucose is <120 mg/dL, consume 15 g of carbohydrates to provide an energy source during exercise. Do not exercise if blood glucose is ≥250 mg/dL and ketosis is present or if glucose is ≥300 mg/dL and no ketones are present. If activity is moderate or strenuous, lasts <90 min, and begins within 90 min of a meal, a reduction in prandial doses of lispro, aspart, or glulisine is warranted. Insulin doses may need to be increased and monitored more frequently during periods of prolonged resistance training or when training occurs in a warm environment. Consume 250 mL of fluids 20 min before exercise to maintain hydration.
During exercise	Monitor blood glucose level every 30 min. Continue fluid intake of 250 mL every 20 min during vigorous exercise. If blood glucose drops to <100 mg/dL during periods of moderate or intense exercise, consume 15 g of carbohydrates every 20-30 min. Consider using a CGM device, which will indicate the directional trend in blood glucose during exercise.
After exercise	Perform SMBG overnight if exercise is atypical. Consider consuming additional slow-acting carbohydrates to protect against exercise-induced nocturnal hypoglycemia. Patients with hypoglycemia awareness should wear a CGM device, which will alert them to impending nocturnal hypoglycemia.

CGM, Continuous glucose monitoring; *SMBG,* self-monitoring of blood glucose.

glucose excursions before, during, and after exercise for patients with T1DM.

Each year, 13,000 Americans are diagnosed with T1DM. Early intervention using an MDI or CSII insulin regimen is likely to minimize patients' long-term risks of micro- and macrovascular complications. Modern insulin formulations and delivery systems allow more patients to achieve their target glycemic and metabolic goals. T1DM is no longer an acute disease with a "death sentence" of 6 months as it was before the discovery of insulin. As our understanding of T1DM pathogenesis expands and our treatment armamentarium becomes more accessible, patients with diabetes are now able to life full and productive lives.

As clinicians, we must give our patients credit for making multiple decisions each day that will ultimately determine their ability to physiologically control glucose levels against incredible odds. We should never chastise our patients or imply that they are "noncompliant" because their glucose levels are poorly controlled. As family doctors, our role is to coordinate care for our patients and to make sure all patients are treated toward success rather than failure. T1DM is a challenging chronic disease. No specialty is better equipped to manage all aspects of diabetes than family medicine.

Long-Term Complications of Diabetes

Prolonged exposure to hyperglycemia, glycemic variability, genetic predisposition, oxidative stress, obesity, environmental factors, duration of disease, and timing of intensive management initiation are important determinants in the development of long-term diabetes-related complications. Microvascular disease resulting in small vessel injury can lead to disorders affecting the peripheral, sensory, and autonomic nerves; kidneys; and eyes. Macrovascular complications damage large vessels, resulting in coronary artery disease, MI, angina, peripheral arterial disease, and stroke. The link between glycemic burden and induction of disease-specific complication pathways has been established to involve four independent biochemical abnormalities: increased polyol pathway flux, increased formation of advanced glycation end products, activation of protein kinase C, and increased hexosamine pathway flux. These seemingly unrelated pathways have an underlying common denominator, which is an increase in oxidative stress caused by the overproduction of superoxide by the mitochondrial electron transport chain (Figure 34-6). Hyperglycemia, whether acute (postprandial) or chronic, has tissue-damaging effects on cell types such as capillary endothelial cells of the retina, mesangial cells in the renal glomerulus, and peripheral neurons. Cells that can effectively assimilate glucose as an energy source before transporting nonessential glucose out of the cell are less prone to complications. Cells such as neurons and nephrons, which are inefficient interstitial transporters of glucose, undergo oxidative stress, which induces endothelial dysfunction, vascular inflammation, and activation of pathways that trigger complications. Other cells, such as those in the GI tract, are more efficient at transporting excessive glucose out of the cell, thereby minimizing the risk of oxidative stress.

Vascular endothelial cells form physical and biological barriers between vessel walls and circulating blood cells, with the endothelium playing an important role in the maintenance of vascular homeostasis. Central to this role is the endothelial production of nitric oxide (NO), which is synthesized by the constitutively expressed endothelial isoform of NO synthase. Vascular diseases, including hypertension, diabetes, and atherosclerosis, are characterized by impaired endothelium-derived NO bioactivity that may contribute to clinical cardiovascular events. Endothelial cells exposed to oxidative stress generate high levels of reactive oxygen species via their mitochondrial electron-transport chain. Susceptible cells activate biochemical pathways

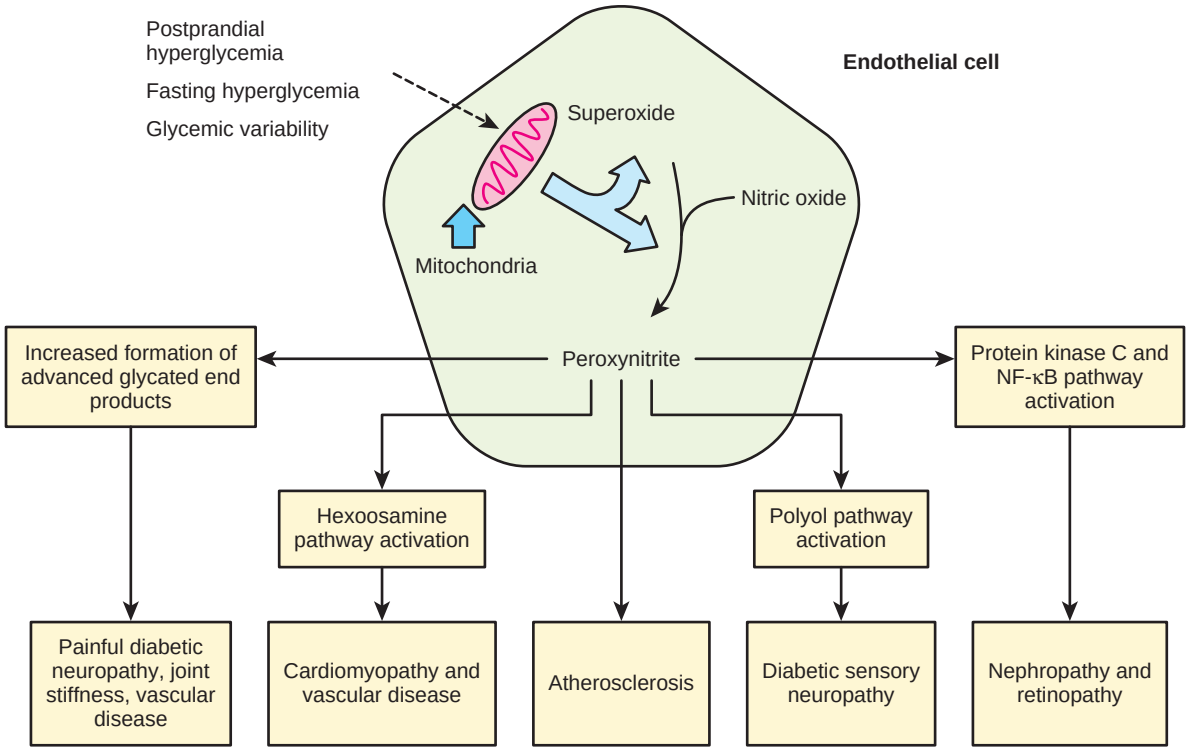

Figure 34-6 Downstream effects of oxidative stress–induced diabetes complication pathways. Postprandial and fasting hyperglycemia, as well as glycemic variability, result in the production of superoxide within the mitochondria of endothelial cells. Nitric oxide regulates vascular tone and minimizes adhesion molecule penetration of the vascular walls. When superoxide interacts with peroxynitrate, the endothelial cell's mitochondrial electron transport system becomes impaired, resulting in endothelial dysfunction. Transcription of endothelial- derived cytokines induce pathways known to activate microvascular complications. Peroxynitrate also favors lipid oxidation leading to atherosclerosis and macrovascular disease. Activation of the protein kinase C and nuclear factor κB pathways favors induction of nephropathy and retinopathy. Neuropathic induction is activated through the polyol pathway. Excessive advanced glycation results in painful diabetic neuropathy. *NF-κB,* Nuclear factor-κB. (Adapted with permission from Unger J. *Diabetes management in primary care.* 2nd ed. Philadelphia: Lippincott, Williams and Wilkins; 2012.)

likely to progress to long-term micro- and macrovascular complications unless metabolic stability is restored.

Brownlee (2001) determined that patients with both acute and chronic hyperglycemia live in a constant state of oxidative stress favoring end-stage complications. Exposure to blood glucose levels greater than 180 mg/dL results in prolonged endothelial cell dysfunction and vascular inflammation that persist for 7 days even after the acute episode of hyperglycemia is reversed. Clinically, patients who record a fasting blood glucose level greater than 180 mg/dL have likely been exposed to oxidative stress that has persisted throughout their resting hours. Failure to recognize and correct the chronic hyperglycemic state will place patients at risk for all-cause mortality and long-term complications.

Tables 34-29 and 34-30 list practical pointers related to each of the major long-term micro- and macrovascular complications observed in patients with diabetes. Table 34-31 summarizes the ADA's recommendations for use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with diabetic nephropathy.

Primary care physicians should play a proactive role in screening patients for micro- and macrovascular complications. All patients with diabetes should be provided with written, individualized glycemic targets for fasting glucose, postprandial glucose, and A1C. Glycemic targets should be determined based on patients' duration of disease, presence or absence of significant comorbidities (especially macrovascular disorders), ability to safely and effectively perform SMBG, history of hypoglycemia unawareness, and psychosocial support mechanisms. Patients with renal insufficiency are at risk for treatment-emergent hypoglycemia and should have their prescription and herbal medications reviewed at each visit. Patients with chronic liver disease should discontinue use of sulfonylureas and consider lowering insulin doses. Chronic liver disease appears to increase β-cell sensitivity to sulfonylureas and reduce hepatic clearance of insulin, both of which can lead to a higher risk of hypoglycemia.

Undoubtedly, diabetes is a very complex disorder that requires a comprehensive treatment plan for most patients. Primary care physicians should not hesitate to communicate with consulting physicians who are co-managing their diabetes patients. Primary care physicians need to develop better means for monitoring their patients for compliance related to their specialty care visits. In addition, clinicians must communicate their concerns about patients' poor metabolic control to co-managing specialists to ensure that patients receive timely and appropriate screening and management of their long-term complications.

Table 34-29 Diabetes-Related Microvascular Complications: Practical Pointers

Complication	Statistics of Interest	Clinical Presentation	Treatment Strategies	Prevention or Reversal
Neuropathy	50% of patients with clinical neuropathy may be asymptomatic Affects 25%-30% of all patients with diabetes Cardiac autonomic neuropathy associated with a threefold increased risk of mortality	Pain derived from small nerve fibers may be sharp, burning, and lancinating Patients describe pain as "bee stings through socks" or "walking on hot coals" Pain typically worse at rest and improves with activity Negatively affects sleep, quality of life, and balance; may lead to anxiety and depressive symptoms Autonomic symptoms include loss of sweating on forehead and feet; abdominal distention; nocturnal diarrhea and constipation; erectile dysfunction and vaginal dryness; orthostatic hypotension; cardiac autonomic dysfunction; and hypoglycemia awareness autonomic dysfunction	FDA-approved drugs include duloxetine and pregabalin Avoid tricyclic antidepressants in patients >65 years of age because of adverse side effects For refractory pain, consider gabapentin + methadone	Smoking cessation Weight reduction Improvement in triglycerides Consider use of vitamin D_3, 4000 IU, and magnesium oxide, 250 mg, at bedtime For autonomic dysfunction, glycemic variability must be minimized and A1C should be brought as closely and safely as possible to the range of 7%-7.5%
Nephropathy	30% of patients with T1DM and 10%-40% of patients with T2DM will eventually develop ESRD Diabetes accounts for 38% of all ESRD in the United States The mean A1C of patients initiating treatment for ESRD is 7.6%, suggesting that risk factors such as genetics, BP, smoking, obesity, and hyperlipidemia may be influential in determining both disease progression and outcomes Diabetes-related ESRD declined in all age groups by 3.9% per year from 1996 to 2006 as physicians became more aware of the importance of intensive metabolic management of glucose, BP, and hyperlipidemia The highest mortality rates are observed with macroalbuminuria (albumin-to-creatinine ratio >300 mg/g) and a GFR <60 mL/min/1.73 m^2	CKD is defined as having an estimated GFR <60 mL/min/1.73 m^2 over 6 months CKD stages are based on the estimated GFR (mL/min/1.73 m^2) as follows: ▪ Normal: >90 ▪ Stage 1: >90 with kidney damage ▪ Stage 2: 60-89 with kidney damage ▪ Stage 3: 30-59 ▪ Stage 3A: 45-59 ▪ Stage 3B: 30-44 ▪ Stage 4 : 15-29 ▪ Stage 5: <15	Discontinue nicotine and alcohol Screen high-risk patients for sleep apnea, vitamin D deficiency, and secondary hyperparathyroidism DCCT: intensively managing T1DM reduces the incidence of microalbuminuria by 39% ADVANCE: 21% reduction in the risk of new or worsening nephropathy noted in patients as systolic BP was reduced to 110 mm Hg ACE inhibitors and ARBs decrease the risk of progression to macroalbuminuria by as much as 60%-70% A moderately low-protein diet (0.9 g /kg/day) used in patients with T1DM and progressive diabetic nephropathy reduced the risk of ESRD and death by 76% without affecting the decline in GFR Drugs that require dosage adjustments in patients with nephropathy include metformin, sulfonylureas, α-glucosidase inhibitors, glitinides, and insulin. The incretin-based therapies exenatide, sitagliptin, saxagliptin, and alogliptin require dosage reductions in people with a creatinine clearance of <50 mL/min; liraglutide and linagliptin require no adjustments. SGLT2 inhibitors are ineffective at estimated GFR <45 mL/min/1.73 m^2 Screen and treat patients for anemia to reduce the risk of heart failure and CKD progression; maintain hemoglobin levels ≥12 g/dL Use aspirin to prevent CVD; higher doses are needed because patients with CKD are aspirin resistant Lowering LDL cholesterol to <100 mg/dL may minimize CVD risk but not CKD progression	Yearly measurements of creatinine, urinary albumin excretion, and potassium

Continued on following page

Table 34-29 Diabetes-Related Microvascular Complications: Practical Pointers (Continued)

Complication	Statistics of Interest	Clinical Presentation	Treatment Strategies	Prevention or Reversal
Retinopathy	Prevalence of diabetic macular edema in the United States is 28% Only 63% of diabetes patients have had screening eye examinations	"Mild" refers to the presence of microaneurysms only. "Moderate" NPDR is defined as the presence of microaneurysms and either hard exudates or blot hemorrhages caused by the deposition of lipoproteins and the exudation of red blood cells from retinal microaneurysms. "Severe" NPDR is characterized by a large number of retinal hemorrhages or the presence of cotton-wool exudates (microinfarcts within the nerve fiber layer of the retina) and the development of intraretinal microvascular abnormalities (collateral vessels) in the resulting ischemic areas of the retina. PDR is associated with the development of abnormal new retinal blood vessels that may bleed into the vitreous cavity and become fibrotic; the resulting traction on the macula leads to visual loss. Diabetic macular edema results in thickening of the retina and decreased central visual activity.	Minimize glycemic variability DCCT: intensive diabetes management reduced risk of proliferative retinopathy by 47% UKPDS: intensive BP control resulted in a 47% risk reduction in vision loss for patients treated to a target of <150/85 mm Hg vs. those treated to 180/95 mm Hg	Screen T1DM patients 3-5 years after initial diagnosis; repeat annually if no retinopathy observed Screen T2DM patients at time of diagnosis; repeat annually if no retinopathy observed Screen before conception and during the first trimester of pregnancy; reevaluate every 1 to 3 months if retinopathy is present Optical coherence tomography can demonstrate intraretinal edema affecting the macula Digital retinal photography allows for rapid acquisition of high-quality retinal images without requiring pupillary dilatation; these cameras can be used by primary care physicians with interpretation by trained ophthalmologists

ACE, Angiotensin-converting enzyme; *ADVANCE,* The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CKD,* chronic kidney disease; *CVD,* cardiovascular disease; *DCCT,* Diabetes Control and Complications Trial; *ESRD,* end-stage renal disease; *GFR,* glomerular filtration rate; *FDA,* Food and Drug Administration; *LDL,* low-density lipoprotein; *NPDR,* nonproliferative diabetic retinopathy; *PDR,* proliferative retinopathy; *T2DM,* type 2 diabetes mellitus; *T1DM,* type 1 diabetes mellitus; *T2DM,* type 2 diabetes mellitus; *UKPDS,* U.K. Prospective Diabetes Study.

Tarantola RM, Maturi RK, Kushal S, et al. Screening, prevention, and ambitious management of diabetic macular edema in patients with type 1 diabetes. *Curr Diab Rep*. 13:679-686, 2013; Unger J. *Diabetes management in primary care*. 2nd ed. Philadelphia: Lippincott, Williams and Wilkins; 2012.

Table 34-30 Diabetes-Related Macrovascular Complications: Practical Pointers

Complication	Statistics of Interest	Clinical Presentation	Treatment Strategies	Prevention or Reversal
Coronary heart disease, stroke, and peripheral arterial disease	The mortality rate at the time of acute MI is essentially doubled in patients with diabetes compared with those without diabetes. For MI survivors, follow-up mortality in patients with diabetes is essentially doubled compared with those without diabetes. 80% of diabetes-related deaths are attributable to coronary heart disease, stroke, and peripheral arterial disease.	Chest pain, shortness of breath, anxiety (in women), orthostatic hypotension, loss of beat-to-beat variability, abnormalities in QT interval (QT prolongation), depression, erectile dysfunction, low testosterone levels in men, fatigue, peripheral edema, congestive heart failure, and sudden death For peripheral arterial disease: ▪ Some patients are asymptomatic ▪ Pain with ambulation; subsides with rest ▪ Hair loss ▪ Brittle nails ▪ Dry, scaly, atrophic skin ▪ Dependent rubor ▪ Pallor with leg elevation after 1 minute at 60 degrees (normal color should return in 10-15 seconds; >40 seconds indicates severe ischemia) ▪ Ischemic tissue ulceration (punched-out, painful, with little bleeding), gangrene ▪ Absent or diminished femoral or pedal pulses ▪ Arterial bruits	Low-dose aspirin Lower LDL cholesterol to <100 mg/dL Lower BP to <130/80 mm Hg Target A1C to lowest and safest level using rational pharmacology to minimize risk of hypoglycemia, especially in patients with T2DM and preexisting coronary artery disease	Screen for and manage risk factors related to unhealthy lifestyle choices: inactivity, obesity, smoking, alcohol, and inactivity. Reduce and slow progression of microalbuminuria and CKD. Recommendations for ABI screening to detect peripheral arterial disease in patients with diabetes: ▪ A resting ABI should be used to established diagnosis of peripheral arterial disease in high-risk patients. ▪ Index is calculated as the ratio of systolic BP at the ankle to that at the arm. ▪ High-risk patients include those with exertional claudication, nonhealing wounds, and age ≥65 years or age ≥50 years with a history of smoking or diabetes. ▪ Normal values defined as 1.00 to 1.40; borderline 0.91 to 0.99. ▪ Abnormal values are ≤0.90.

ABI, Ankle-brachial index; *CKD,* chronic kidney disease; *MI,* myocardial infarction; *LDL,* low-density lipoprotein; *T2DM,* type 2 diabetes mellitus.

Rooke TW, Hirsch AT, Misra S, et al. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 124:2020-2045, 2011; Fowler MJ. Complications of diabetes. *Clinical Diabetes.* 29:116-122, 2011; Unger J. *Diabetes management in primary care.* 2nd ed. Philadelphia: Lippincott, Williams and Wilkins; 2012

Table 34-31 Treatment for Diabetic Nephropathy

Category	Recommended Treatment
T1DM or T2DM with micro- or macroalbuminuria	ACE inhibitors or ARBs
T1DM with hypertension and albuminuria	ACE inhibitors delay progression of nephropathy
T2DM with hypertension and microalbuminuria	ACE inhibitors or ARBs delay the progression to macroalbuminuria
T2DM with hypertension, macroalbuminuria, and renal insufficiency (serum creatinine >1.5 mg/dL)	ARBs delay the progression of nephropathy
T1DM or T2DM with microalbuminuria and normal BP	ACE inhibitors or ARBs

ACE, Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *T1DM,* type 1 diabetes mellitus; *T2DM,* type 2 diabetes mellitus.

References: American Diabetes Association. Clinical practice recommendations, 2011. *Diabetes Care.* 34(suppl 1):S33, 2011; Gross JL, de Azevedo MJ, Silveiro SP, et al. Diabetic nephropathy: diagnosis, prevention and treatment. *Diabetes Care.* 28:164-176, 2005.

Table 34-32 Five Key Behaviors to Help Patients Become Successful Diabetes Self-Managers

1. Know your metabolic targets (A1C, BP, and lipids).
2. Know how to achieve your metabolic targets.
   a. Increase physical activity.
   b. Consume a healthy diet.
   c. Perform SMBG in a timely manner.
3. Stop smoking and alcohol use.
4. Take your prescribed medications.
5. Be certain your health care providers understand how to successfully and intensively manage diabetes.

BP, Blood pressure; *SMBG,* self-monitoring of blood glucose.

Five Things Patients Must Do to Become Successful Diabetes Self-Managers

A diagnosis of diabetes presents numerous challenges for patients, their families, and the clinicians who direct their care. At times, the burden of having diabetes may seem overwhelming. Unfortunately, diabetes is a chronic disease requiring daily adjustments in care and, in most cases, adoption of intensive lifestyle alterations. Rather than increase their concern about the future risk of long-term complications, newly diagnosed patients with diabetes should be reassured that their lives can be long, productive, and healthy if they adopt the five specific behaviors listed in Table 34-32. Of primary importance is reassuring patients

that the number 1 complication of *well-controlled* diabetes is ... nothing!

Acknowledgment

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Videos

The following video is available at www.expertconsult.com:

Video 34-1 Demonstration of the Use of Selected Equipment Used in the Management of Diabetes

References

The complete reference list is available at www.expertconsult.com.

Web Resources

www.cdc.gov/diabetes/ Centers for Disease Control and Prevention. National Diabetes Fact Sheet provides general information and national estimates on diabetes in the United States.

www.endotext.org/ Endotext. Up-to-date, comprehensive source of information on all topics in clinical endocrinology.

www.who.int/diabetes/facts/en/ World Health Organization. Diabetes program fact sheet.